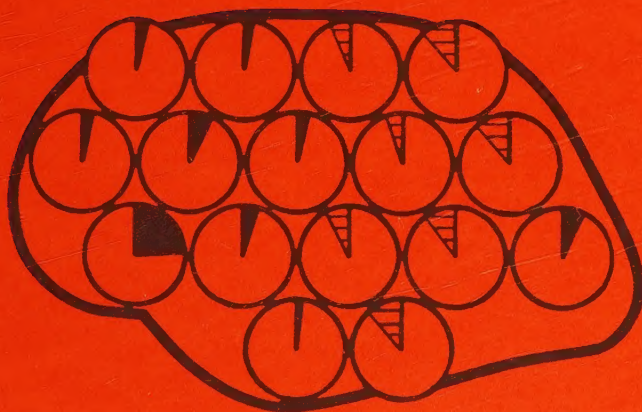


MAPPING BRAINWORK

Theoretical and Methodological Considerations
in Applying the Regional Cerebral Blood Flow
Method to Neuropsychology

Isak Prohovnik



Lund 1981

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The thesis is based on the following six papers, referred to in the text by roman numerals:

- I. Maximilian, V.A., Prohovnik, I. and Risberg, J. Cerebral Hemodynamic Response to Mental Activation in Normo- and Hypercapnia. Stroke, Vol 11, No 4, 342-347, 1980.
(pp. 39 - 45)
- II. Jablonski, T., Prohovnik, I., Risberg, J., Staahl, K-E. and von Sabsay, E. Fourier analysis of ^{133}Xe inhalation curves: Theory and Implementation. In Clinical Applications of Non-Invasive Xenon Studies in Cerebral Blood Flow, R.H. Ackerman, W.D. Obrist (eds.) The Williams and Wilkins Company, Maryland, U.S.A.. In press.
(pp. 47 - 56)
- III. Prohovnik, I., Risberg, J. and Jablonski, T. Fourier analysis of ^{133}Xe inhalation curves: Preliminary Empirical Validation. In Clinical Applications of Non-Invasive Xenon Studies in Cerebral Blood Flow, R.H. Ackerman, W.D. Obrist (eds.). The Williams and Wilkins Company, Maryland, U.S.A.. In press.
(pp. 57 - 70)
- IV. Prohovnik, I., Håkansson, K. and Risberg, J. Observations on the functional significance of regional Cerebral Blood Flow in "resting" normal subjects. Neuropsychologia, Vol 18, 203- 217, 1980.
(pp. 71 - 85)
- V. Prohovnik, I., Risberg, J., Hagstadius, S. and Maximilian, V.A. Regional cortical activity during perception: Visual tasks of increasing complexity.

Submitted for publication, 1980.

(pp. 87 - 109)

VI. Prohovnik, I., Risberg, J., Maximilian, V.A. and

Hagstadius, S. Regional cortical activity during perception: Lateralized tactile sensation and attention.

Submitted for publication, 1980.

(pp. 111 - 138)

Paper I shows the separability of mental activation from purely vascular factors in the normal human brain. Papers II and III are the first detailed publications of a new analysis method, shown to be more sensitive than the conventional method. Paper IV describes the resting state of rCBF from methodological and neuropsychological points of view. Papers V and VI are neuropsychological studies of visual and tactile perception, by means of rCBF and the new analysis method.

INTRODUCTION

"The problem is indeed formidable: What common units can be applied to such activities as conversing, driving a car, memorizing lists, and observing pictures?"

(Kahneman, 1973)

"Human neuropsychology is the study of neural mechanisms underlying human behavior. The discipline is based on a systematic analysis of disturbance of behavior following alterations of normal brain activity by disease, damage, or experimental modification."

(Hecaen and Albert, 1978)

The problem has been formidable indeed, but the present thesis is intended to show that we now may be very close to finding these long-awaited common units. And since we may find and observe them in an intact, normal human brain we can soon, perhaps, modify our definition of neuropsychology into a discipline that is no longer almost totally dependent on observations of a malfunctioning brain in order to understand the healthy one. This thesis will attempt to describe the current state of a measurement technique, delineate its interface with human neuropsychology, and carefully avoid the very tempting digression into the realm of the mind-body issue.

The technique which is central to the thesis is the measurement of regional Cerebral Blood Flow (rCBF) by means of the ¹³³-xenon inhalation method. It will be introduced by short reference to other available techniques and then briefly described; more detailed descriptions can be found in literature mentioned in the text, especially a recent

review by Risberg (1980). A detailed discussion of methodological and theoretical issues pertinent to neuropsychological applications will follow, centered mostly on the six papers on which the thesis is based.

Let the purpose of neuropsychology, or some branch thereof, be defined as the localization and quantification of neural activity in the human brain which is associated with behavior in a differential and predictable way. This association may or may not be interpreted causally, depending on one's philosophical inclinations and the limitations of current knowledge. In order to achieve that purpose we need to observe behavior, observe neural activity or its absence, ideally quantify each and derive their relationship. For present purposes, current techniques of "neural observation" may be divided into those applicable in animals only and those that may be used in man. Orthogonal to the species-applicability dimension is another, on which we can rank techniques as primarily morphological or primarily functional. Lastly, one must consider a method's invasiveness, i.e., the degree to which the observation modifies the observandum and, in man, there is obviously the consideration of invasiveness as a possible risk or trauma for the subject. With respect to the first dimension, it is generally agreed that extrapolating from animals to man is inferior to observations of humans, and for the present analysis animal studies do not play a central role, although they have until now been indispensable and immensely productive. As for methods applicable in man we may ignore the ones that are primarily morphological; although

some of them are wonderfully useful, we are interested in neural function and would rather observe it directly than infer it from morphology. We are left with methods that localize and quantify function in human brains. In this set, the most prominent source of neuropsychological knowledge has without question been the study of brain-damaged patients. It is generally conceded, however, that extrapolation from a malfunctioning brain to a healthy one is risky (e.g., Whitaker, 1978), so we need something better, a method that can be used for investigating neural function in a normal human brain. Until recently this limited the field to electrophysiology, represented mostly by the EEG but also other derived variables (perhaps the best known are the so-called Evoked Potentials and Contingent Negative Variation). These are certainly applicable in the normal human subject and they are totally noninvasive; the problem is that with the exception of narrowly-defined special purposes, mostly clinical, their information content is quite low. The issue has recently been discussed elsewhere (Gevins et al., 1979 a,b) and most workers would probably agree with Ingvar et al. (1976) that electrophysiological findings are "often difficult to interpret, and they cannot be translated into mass activity terms or into psychophysiological concepts", mainly due to their obscure underlying mechanism and poor spatial resolution. Regional CBF is a technique which combines all of the requisite properties. It provides a method of observing neural function in a normal, intact human; although it is noninvasive, it yields localized and quantitative "common units" with clear physiological origins and directly trans-

latable behavioral implications.

The origin of the rCBF technique can be dated to about 35 years ago (Kety and Schmidt, 1948). Regionality was first achieved about twenty years ago (Lassen and Ingvar, 1961), and soon thereafter the first neuropsychological observations were made by means of this tool (Ingvar and Risberg, 1965). Other crucial attributes, such as non-invasiveness and bilaterality were conceived at about the same time (Veall and Mallett, 1966), but the great majority of neuropsychological work continued with the unilateral carotid injection method (Ingvar and Risberg, 1967; Risberg and Ingvar, 1968; Ingvar and Gustafson, 1970; Olesen, 1971; Risberg and Ingvar, 1973). The modern inhalation technique first achieved recognition as a neuropsychological tool five years ago, with the publication of two papers of major importance by Obrist et al. (1975) and Risberg et al. (1975a). The first showed its feasibility, and the second showed its neuropsychological potential.

There are two facts of crucial importance for the technique. The brain performs work at the expense of metabolic energy, and since there are practically no stores for metabolic substrates in the brain these substrates must be continuously supplied by cerebral blood. Consequently, increases of metabolic activity must be closely coupled to increases of cerebral blood flow. For a detailed treatment of this complex issue, the reader is referred to Siesjö (1978).

Although the metabolic-flow coupling has been assumed for a long time, it is only recently that it has been directly demonstrated. Raichle et al. (1976) measured the regional metabolic rate for oxygen ($rCMRO_2$) and rCBF in neurologically normal patients and in patients with chronic, stable brain damage. In both groups rCBF correlated well with $rCMRO_2$ (both measured by the ^{15}O technique). In one patient, they demonstrated parallel regional increases of flow and metabolism during hand movement, thus showing that even temporary changes of local metabolism are coupled to local flow. High-resolution animal studies have extended the coupling of metabolism-flow-neuronal activity down to the very basic functional level of individual cortical columns (Heiss et al., 1979; Hand et al., 1979; Greenberg et al., 1979; Tsubokawa et al., 1980). These columns, with a horizontal diameter of a few hundred microns, may well represent the smallest cortical unit of meaningful information processing (Szentagothai, 1975).

The common units that Kahneman (1973) was seeking are thus, ultimately, the quantified work being performed by neurons in the human brain. It is probably not controversial to state that all the activities mentioned in the first quote (Kahneman, 1973) are associated with unique patterns of neural activity, and that these patterns may be distinguished from each other both qualitatively (according to their distribution over different areas of the brain) and quantitatively (according to the intensity of activity). Measurements of rCBF, thus, by reflecting neuronal metabolism, yield a quantitative map of the way in which the human

brain solves problems and controls behavior. And if we can measure rCBF in the intact, normal human brain, then we have a possibility of extending neuropsychology into a science of normal human behavior.

Inhalation rCBF is one of a large class of techniques employing radioactive tracers. Body tissues are relatively transparent with respect to some forms of electromagnetic radiation emitted by these tracers, and thus their concentration in the body and movement through it can be recorded by externally-placed detectors. If the tracer's concentration can be predictably related to some physiological process in the body, then that process can be measured by the detectors. The gamma-emitting tracer used by the inhalation rCBF technique is a very common one, $^{133}\text{-xenon}$. It is chemically inert, and thus does not interfere with the observed processes. Additionally, it is freely diffusible across the walls of blood vessels, specifically the brain-blood barrier, its movements determined only by simple concentration and solubility relations.

The main features of the inhalation rCBF method have recently been described by Risberg (1980) and therefore only a basic summary will be given here. The theory and mathematics are outside the scope of the present thesis, as are the radiophysical aspects; the interested reader is referred to basic publications by Zierler (1965), Obrist et al. (1967), Lassen and Ingvar (1972), Obrist et al. (1975), Risberg (1980) and paper II included here.

All work reported here was conducted with a standard rCBF system with 32 detectors placed over both cerebral hemispheres. Subjects were lying supine, breathing through a face-mask. A single measurement lasted 11 or 16 minutes, and each subject was measured 1-8 times with different intervals and conditions. Data were analysed by a computer according to principles developed by Obrist et al. (1975), Risberg et al. (1975b) and Jablonski et al. (paper II). Flow values are derived by a bicompartmental analysis as two parameters; f_1 and ISI, both considered to represent blood flow largely through the grey cortical matter.

THEORY AND METHODOLOGY

Anatomical Validity

A serious limitation of present rCBF techniques is the lack of certainty regarding the cortical region "seen" by each detector. This problem is multileveled; it is due to variance in head size and shape, the relation between skull landmarks and brain location, variance in brain size and shape, and finally the variance of functional localization and organization in different brains. This thesis incorporates a modest attempt at solving the first two levels, described in paper IV. Ideally, the procedure described there would fixate three of our detectors over the Rolandic strip; assuming a fairly constant relation between this area and the rest of the cortex in human brains, this would also fixate all other detectors in relation to cortical loci since all 16 detectors covering one hemisphere are held by a common detector block. This simple procedure can

be supplemented by relating detector positions to two other commonly-used landmarks, the external auditory meatus and the nasion. A more reliable way of localizing the Rolandic strip was successfully demonstrated by Lassen and his collaborators. By using basic sensorimotor tasks (for example stereognosis by the mouth, hand and foot, Roland and Larsen, 1976) one can actually see the central strip in rCBF maps, if one has the spatial resolution that these investigators use; this is still beyond our current system's capacity. However, establishing the location of the central fissure does not eliminate the problem at the next two levels: Individual brains may differ in size, shape and relations of cortical structures (demonstrated for the temporal lobe by Campain and Minckler, 1976) and moreover, function may be variably localized in the same structure for different individuals. Thus, one finds variance in functional localization even under the ideal conditions of electrical stimulation of an exposed cortex in a patient undergoing surgery (Ojemann and Whitaker, 1978).

We have verified the detector placement procedure constructed in paper IV by marking some detector locations with lead and taking skull x-rays. This has been done in five patients until now, and the relation between the brain contour and detector markings seen in the x-rays fully confirm the drawing shown in papers IV, V, VI. However, we are aware that these drawings are approximate and average. Although our present system represents the highest spatial resolution currently available, it is far from the limits of error imposed by anatomical variance. However, a double-

resolution inhalation system is presently under construction by Ingvar's group, and no doubt this trend will continue. In neurophysiological terms, the ultimate aim is probably the cortical columnar units with diameters of 200-300 microns. But both anatomical considerations (Szentagothai, 1978) and behavioral observation during electrical stimulation of the cortex in conscious patients (Ojemann and Whitaker, 1978) suggest that cortical organization on a neuropsychologically meaningful level may consist of much larger units, with diameters of several millimeters. This is still beyond the resolution offered by available rCBF instrumentation, but it does not seem unattainable with foreseeable technological development. Anatomical validity and variability may prove to be the ultimate limitation of rCBF, rather than technical obstacles.

Physiological Validity

Most aspects of the physiological validity of the inhalation rCBF method have been recently dealt with by Risberg (1980). The material presented here sheds more light on the issue of crosstalk, and mostly on the method's sensitivity. Crosstalk refers to the likelihood that a detector aimed at one hemisphere will be influenced by radiation from the other hemisphere. The homologous correlations presented in paper IV and the contralateral effects reported in paper VI both confirm previous indications (Risberg, 1980) that crosstalk effects are not of a destructive magnitude, and cannot completely obscure significant effects. Asymmetries are undoubtedly underestimated by the inhalation rCBF method and other bilateral, two-dimensional single-photon

techniques, but with careful design and procedures they are not obliterated (c.F. Risberg et al., 1975a).

A previous major weakness of the inhalation rCBF method (Risberg, 1980) was its low sensitivity to high flows, especially when these occurred in small tissue volumes. This limitation was especially severe for neuropsychological research in normal subjects, since in clinical practice interest often centers on regions with abnormally low flow. The low sensitivity was caused mainly by the inability of the conventional analysis (Obrist et al., 1975) to utilize the full clearance curve, and this problem is now largely resolved by the new Fourier analysis (paper II, III). The data of papers V and VI were analysed by both methods, and Fourier analysis was found to be much more sensitive in paper V, but only slightly more sensitive in paper VI. We do not yet have full data for a rigorous comparison, but these differences might be modality specific: Maximilian (unpublished data, 1980) found a slight superiority of Fourier analysis in an auditory task, comparable to the magnitude of differences in our tactile task. Additionally, the ISI flow index (Risberg et al., 1975b) with the conventional analysis is seen, in preliminary comparisons, to be much less sensitive than either f_1 or the Fourier ISI, which is computed during a much earlier period. Risberg (1980) pointed out the likelihood of highly heterogeneous flow components in activated tissue, a possible basis for the large sensitivity differences in the visual modality. Similarly large sensitivity differences were found in paper III in epileptic tissue, with indications of small tissue

volumes with high flows. Tentatively, thus, it seems that the conventional analysis may be expected to be only slightly less sensitive when flow is homogeneously high throughout the examined tissue, and the sensitivity advantage of Fourier analysis would be inversely proportional to the relative size of the fast-flow compartment. Alternatively, it is possible that activation responses may be differentially distributed over time. Both analysis-methods would be sensitive to flow that is enhanced throughout the recording period (or at least in the first few minutes) but only Fourier analysis can discover flow components that are active in the beginning and disappear quickly. This disappearance would occur either because flow is so fast that the compartment is almost instantaneously emptied of tracer, or because the activation itself disappears, perhaps due to habituation. There is nothing very surprising in these assumptions, but it then follows that there may be a fundamental difference in the neural organisation of the three major sensory systems in human cortex. For example, the visual system would seem to consist of highly interlaced heterogeneous subsystems, whereas the auditory and tactile modalities would be organized in more homogeneous units. Some support for the heterogeneity of the visual system is cited by Risberg (1980); the generation of more precise hypotheses on the composition of the three modalities must await a careful examination of our flow results with both methods of analysis.

A different problem emerged, however, during the data collection for this comparison: The conventional analysis,

although insensitive, is very stable and reliable. The Fourier analysis appeared to yield data with higher variance, and to have a consistent tendency to overestimate flow in certain areas. This systematic overestimation did not seriously impair sensitivity, as shown by the occipital pole region in paper V, but it indicated some error. These effects were totally absent from data collected in an extensive simulation testing, described in paper II. The indicated conclusion was, therefore, that the mathematical model and its underlying physiological assumptions were incorrect. And since the errors were not present in the Obrist analysis, which ignores the initial parts of the clearance curves, it seemed likely that the error arose there. Careful examination of physiological curves and more computer simulation resulted in a likely solution which is now undergoing final testing (Prohovnik et al., submitted).

The original model for the Fourier analysis assumed one artifactual source of counts, originating from air in the nasopharyngeal cavities and with a concentration function identical in shape to the averaged air curve. We have found this source to account for most of the artifactual counts, but not all. The other source was found to have a concentration function shaped like the end-tidal air curve, which is an effective estimate of arterial concentration (Obrist et al., 1967). Changing the basic model to account for these two artifacts, instead of one, improves curve fitting at the early parts and eliminates the flow overestimation. Since this second artifact represents fairly high frequencies, its omission from the earlier model caused

these high-frequency components to be interpreted as part of the fast flow compartment, and probably to increase the variance of the results. We do not have enough data yet to map its distribution as we have done for the first artifact (paper III) and to estimate the resulting variance reduction.

A third aspect of physiological validity was studied in an experiment described in paper I. The results show that flow changes associated with mental activity (in this case, Raven's Advanced Matrices test) were constant in two different physiological conditions involving the cerebral vasculature. Aside from the highly evident test-retest reliability shown, this finding suggests that one can safely compare rCBF changes from different baseline levels, if these differences in baseline levels are caused by general vascular factors. The situation is probably different when the baselines differ with respect to metabolic levels: In a previous publication (Risberg et al., 1977) we showed that task-related flow increases were negatively correlated with resting flow levels.

Statistical Issues

Compared to other neuropsychological research areas, one of the major weaknesses of rCBF is in the area of statistical analysis and inference. One of the reasons for this weakness is the richness of data supplied by multidetector rCBF systems, with the complex relationship among brain areas, flow parameters, two hemispheres, etc. A good discussion of statistical problems typically associated

with rCBF has recently been published by Wood (1980), and one of the points noted there was the possibility of distorted distributions, and the resulting recommendation to use non-parametric statistics. It is our experience, however, that problems such as skewed distributions, large variances and correlations between means and variances are usually associated with mathematical failures of analysis, technical errors and the instability of bicompartamental solutions. A discussion of these sources of error is outside the scope of this thesis, but two points should be mentioned. The first is the very clear superiority of the Risberg ISI to any bicompartamental parameter as a reliable variable, and the second point pertains to the nature of some reliability criteria.

Paper IV was designed as a methodological experiment, with the aim of investigating the statistical properties of rCBF variables over time. In addition to standard descriptive statistics, reliability was studied by a 2-way analysis of variance design, with subjects and measurements as the two factors. The ISI parameter was found to be overall superior to all other parameters in all experimental groups: It was most reliable, least deviant from normality, with lowest variance. It was also mathematically more valid; even even in cases where - due to some error - the bicompartamental analysis was obviously wrong, the ISI still yielded a reasonable estimate of flow (this phenomenon is often seen in clinical situations). The other commonly-used parameter, f_1 , was clearly inferior in reliability. However, when we examined the regional distribution of reliability

estimates we found that the most reliable regions were anterior temporal and inferior frontal, and also the posterior parietal locations; the common denominator of these regions is their peripheral location. Additionally, we found that average flow levels were highly variable among individuals but highly consistent throughout the measurement series; the opposite was true for the regional flow patterns, expressed as percent deviation from hemispheric means.

The problem that arises when one interprets these findings is whether stability under these conditions should be termed reliability or insensitivity. The nature of the resting state is treated at length in paper IV, with the conclusion that we cannot expect a "resting" human being to show perfectly stable rCBF: The psychophysiological activity of the human cortex is in no way comparable to physiological homeostatic variables such as body temperature (and even body temperature shows circadian rhythmicity). As shown by Ingvar and Philipson (1977) for imagined movement, Risberg (1980) for hallucinations and Prohovnik et al. (paper VI) for attentional sets, subjective states can powerfully affect rCBF in the absence of observable external events. The high reliability of flow in peripheral regions may reflect individual anatomical characteristics, such as head size and shape. It is, thus, possible that some part of the reliability shown by such analysis of repeated studies should be interpreted as insensitivity to valid functional changes.

A comment on the statistical techniques used in paper I, VI, V, and VI: Whether rCBF data comply with the assumptions of analysis-of-variance models is a question that can probably be determined, given sufficient data and experience. However, we are already aware of a definite flaw in these analyses, namely, the treatment of each detector as a separate variable. As clinical and research practice very often demonstrate, and as Wood (1980) pointed out, rCBF changes should be analysed as patterns: Relations among detectors must be taken into account. During the last years we have progressed from t-tests to the current repeated-measures analysis of variance. The next step is planned to incorporate multivariate analysis of variance, treating each hemisphere as a single vector of 16 variables.

Local and General Activation: Further Elucidation of Hyperfrontality

Risberg and Ingvar (1973) were probably the first to draw attention to the existence of two qualitatively different factors in rCBF, local and general. The general factor, presumably affecting all regions equally, was noted to be highly variable across subjects and was hypothesized to be related to emotion and anxiety. Local factors were more homogeneous across subjects, being largely task-determined, and appeared only in task-related areas. The general factor was assumed by these authors to be mediated by the reticular system. We have since confirmed these observations several times, including a formal factor analysis of

resting flow data (Prohovnik, unpublished data).

In terms of general and local factors, there seems to be a major difference between the visual experiment (paper V) and the tactile (paper VI). Although in both experiments mean hemispheric flows (ostensibly reflecting the general factor) increase with task complexity, in paper V they do so by virtue of the combined local effects: As more regions are activated, and more intensely, their mean follows. But in paper VI, during the AttBi and AttLt conditions, we see both types of effects: There are local flow increases, but superimposed on them is a clear general, diffuse flow increase that affects all regions, i.e., a true general activation. A detailed comparison of the results (paper VI and V) leads to the postulation of two frontal components of general activation.

We have previously hypothesized (paper IV) that the well-established hyperfrontality of normal rCBF is composed of two components, one superior frontal and the other inferior frontal. This hypothesis was based only on three published studies of the resting state, but can now be extended and supported by activation studies; not much empirical material exists, however, because few laboratories have spatial resolution like ours or better. In the following discussion we will refer to the superior and middle frontal gyri as superior frontal (SF, corresponding to our detector locations 2, 4, and 5) and the inferior frontal gyrus and the temporal pole as fronto-temporal (FT, corresponding to detector locations 3, 6, and 8).

It is suggested that mean hemispheric flow increases in rCBF studies can be associated with increased activity of either frontal system, or both. In the experiment described in paper V, the simplest condition was associated with local increases in the SF system only, and hemispheric means were increased by about 5%. The second complexity level (RotSp) showed no increases of SF, minimal increases of the FT system and 2% enhancement of the hemispheric means. The most complex condition showed increases of both frontal systems and a large increase of hemispheric mean flows (from 7 to 12%). In the tactile experiment (paper VI) again the simplest condition was associated only with increases in the SF system but the most complex condition showed increases of FT only; hemispheric means reacted to both. Additionally, the general activation in paper VI occurred only in association with the FT system activation. These observations suggest that 1) with both modalities and the different tasks involved, the SF system was activated even by the simplest activation procedures, whereas the FT was only involved with the most complex and difficult level, and 2) only when the FT system was involved could we see a true activation of a diffuse general factor.

The first hypothesis implies that under all conditions, activation of the SF system should precede FT activation with increasing task complexity and/or difficulty. Aside from the two studies reported here, there is good support in a paper by Ingvar (1976) which contrasts seven different activations: Two levels of electrical thumb stimulation (sub- and suprathreshold for pain), hand movements, talking, rea-

ding, performing the digit-span backwards test, and Raven's Advanced Matrices test. Every one of these shows activation of the SF system, but only Raven's Matrices test elicits a minimal FT activation. This test can easily be hypothesized to be the most complex of the list, and similar results have been published by us (Maximilian et al., paper I) with intermediate activation (averaging about 5%) in the FT system during the same test. Orgogozo and Larsen (1979), using a high-resolution carotid injection system, studied the supplementary motor area in five patients; in our system this area is included in the SF. Orgogozo and Larsen found in these patients support for a role of the supplementary motor area in sequential movement, but not simpler forms of motor behavior. It is, thus, likely that finer gradation of activation can be found within the SF area and in the low range of very simple behavior.

No published report could be found to support or refute the second hypothesis, relating the FT system to true general arousal, other than our own studies. Some clinical cases, however, studied by Risberg and Gustafson (1977) and diagnosed as Pick's disease, did show a striking difference in flow levels between the SF and FT systems, suggesting that these two systems may be dissociated by some pathological conditions (at identical detector locations as defined on the basis of the present experiments). Similarly, Nilsson et al. (1977) studied paranoid patients before and after 2-3 week administration of haloperidol. These authors found, in the six patients that showed the best clinical medication effect, a flow reduction in the FT system (especially

on the left side) without change in the SF system; again, the division between the detector locations with and without effect in that study is identical to the division seen in papers V and VI.

Anatomically, there is nothing surprising about the proposed division of the frontal lobes, and much smaller subdivisions have been established with different functional roles (e.g., Stamm, 1973). Both the SF and the FT systems have been known to exist for a relatively long time, and are known to have different functional characteristics. The SF system receives input from all major sensory association areas and is intimately connected with the basal ganglia, thalamus and reticular system; it is involved in attention and many poorly-understood input-output control functions (McCulloch, 1948; Nauta, 1971; Gerbner, 1973; Grueninger and Grueninger, 1973; Pribram, 1973; paper VI). The FT system is known to be associated with autonomic functions, affective behavior, and other forms of general control of behavior, often inhibitory (Livingstone et al., 1948; Nauta, 1971; Passingham and Ettlinger, 1972; Sauerland and Clemente, 1973; Jouandet and Gazzaniga, 1979).

Functionally, however, we seem to have come one step further in understanding normal human rCBF within the limits of our present resolution. Hyperfrontality is not a homogeneous phenomenon of the frontal lobe, but a reflection of at least two separate systems. Activity of these systems is associated with whole-brain activity, as measured by the

hemispheric mean flow, but in different ways. Superior frontal areas are correlated with mean hemispheric flow because almost any information-processing task, in any modality, activates them through the converging pathways shown by Jones and Powell (1970). These areas are probably involved with attentional components of the task (together with parietal regions) and other task-oriented functions which are not yet well-understood. On the other hand, inferior frontal, anterior temporal and limbic regions are only activated by the upper range of effort or complexity (Pribram and McGuinness, 1975) and are person-oriented, rather than task-oriented. Their specific involvement is correlated with a true general activation factor which affects all regions equally and is related to affective states.

FINAL COMMENT

As a noninvasive neuropsychological tool for observing localized neural activation in intact humans, the rCBF technique is unique. It is, however, far from perfect and several of its limitations have been mentioned. Two exciting areas currently under active development are measurements, using present technology, of flow in the brain-stem and cerebellar areas by Meyer and his associates (e.g., Juge et al., 1979), and three-dimensional measurements of all cerebral regions, including deep subcortical structures (Kanno and Lassen, 1979; Reivich et al., 1979; Ackerman et al., 1980; Rusineck et al., 1980).

The contribution of papers I-III to neuropsychological

applications of rCBF has been described in the section on physiological validity. The contributions of the other three papers are of three types. The first concerns those with inhalation rCBF that fully agree with previous findings by other methods. They enhance one's trust in the technique, but do little more. The second type includes the findings which are not predicted by current knowledge, although not inconsistent with it. Their validity and importance must be judged by the amount of new research they generate, and by their future refutation or confirmation.

It is the third set of findings which seems best to demonstrate the value of rCBF, and the prominent example is the lateralized attentional activation in paper VI. As described in the paper, there is a considerable amount of previous research, based on other methods, which could have predicted the results. However, none of the previous findings by themselves seem as convincing as those of rCBF, which supply a direct and critical test of the hypothesis. The point is not that our results and interpretation are infallible; further work may, theoretically, refute them. The point is that a well-designed rCBF study is capable of providing critical information for hypothesis-testing that is difficult, if not impossible, to obtain from normal humans by any other method.

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**Cerebral Hemodynamic Response
to Mental Activation in Normo-
and Hypercapnia**

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Cerebral Hemodynamic Response to Mental Activation in Normo- and Hypercapnia

V. ALEXANDER MAXIMILIAN, PH.D., ISAK PROHOVNIK, M. SC., AND JARL RISBERG PH.D.

SUMMARY Changes of regional cerebral blood flow from rest to mental activation by a visually presented spatial reasoning test were measured during normo- and hypercapnia in 10 healthy subjects. Hypercapnia, elicited by inhalation of 6% CO₂, resulted in similar flow increases in all 32 cortical regions measured. Increases of flow during testing were seen in post-central regions of the brain whether the resting level was augmented by hypercapnia or not. The results show that an elevated local functional level in the cortex causes an automatic local vasodilatory response which is totally independent of the basal level of perfusion and availability of metabolic substrates.

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MENTAL WORK leads to regional cerebral blood flow (rCBF) increases in specific cortical areas considered to be functionally active during performance of the task.¹⁻⁴ These changes in flow are directly coupled to variations of regional cerebral metabolic rate of oxygen (CMRO₂) indicating a local level of neuronal activity.^{5, 6} Although cerebral circulation increases as a result of a higher CMRO₂, this relationship is not reciprocal. While CBF is globally increased during hypercapnia,⁷ and hypoxia,^{8, 9} CMRO₂ remains constant within PCO₂ levels of 15–80 mm Hg.¹⁰

By superimposing local metabolic activation, by means of a mental task, upon a globally increased cerebral circulation due to hypercapnia, the relationship between these 2 regulatory mechanisms was investigated in the present study. Two possible outcomes were considered: 1) An rCBF increase as a result of mental activation added to the hyperperfusion caused by hypercapnia, or 2) no further increase due to the already high CBF, the tissue being sufficiently supplied.

Another aim of the investigation was to define the lateralizing properties of visual-spatial problem solving (Raven's Matrices) and to test the reliability and reproducibility of the regional activation response.

Material and Methods

Measurements of rCBF were made in 10 right-handed healthy male volunteers (mean age 26 ± 4 years) by the ¹³³Xe inhalation technique¹¹ as modified by Obrist.^{12, 13} Our ¹³³Xe inhalation system (Medi-tronic-Novo Diagnostic Systems, Denmark) enables simultaneous measurements of 16 homologous regions of both hemispheres by 32 scintillation detectors (¾" × ¾" NaI (Tl) crystals; lead collimators 20 mm deep and 22.5 mm wide) placed in parallel at a right angle to the lateral surfaces of the head. ¹³³Xe mixed with air (2.5 mCi/l) was inhaled by the subjects through a tight-fitting mask and a rebreathing spirometer system for one min followed by 10 min of breathing air.

The first measurement in each subject was preceded by a 30 sec background registration, with a 5 min recording of remaining activity preceding each subsequent measurement (fig. 1). A separate detector continuously recorded radiation in a sample of expired air (via a catheter in the face mask). End tidal values were later used to correct for recirculation.¹² An additional scintillation detector continuously monitored possible leakage of ¹³³Xe from the face mask. A window setting of the pulse-height analyzers was 65–95 KeV. Fourteen bit binary registers integrated counts during 5 sec epochs for the head detectors and during 0.3125 sec periods for the air curve detector. Peak count rates of approximately 500 cps were recorded for the head curves while 1500 cps were obtained for the end-tidal values of the air curve. Using computer programs developed by Obrist and Risberg, the paper tape punched data (Facit, Sweden) were later analyzed by an HP 9825-A desk top computer system, solving, among other variables, for f₁, the flow of rapidly perfused grey matter compartment, and ISI (Initial Slope Index).¹⁴ The arterial PCO₂ was estimated from recordings of end-tidal CO₂ concentrations (Beckman LB₃ analyzer) and blood pressure was measured by auscultation. (For a more detailed description of the ¹³³Xe inhalation technique, see Obrist et al.^{12, 13} and Risberg.¹⁵)

Experimental Design

Each subject had 4 consecutive measurements consisting of counterbalanced rest and problem solving activation during both normal breathing and inhalation of 6% CO₂ mixed with air. The CO₂-air mixture was administered for one min prior to the ¹³³Xe inhalation, discontinued for technical reasons during the one min isotope intake, and recommenced for an additional 8 min (fig. 1).

Before the experiment, each subject was informed in detail about the measurement procedure and the possible discomfort of CO₂ breathing. Each was instructed on the activation test and given at least 3 training items to exercise problem-solving strategy. Subjects were allowed to become accustomed to the experimental situation (breathing in a face mask, supine position with head immobilized by the detec-

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¹³³Xenon inhalation measurement procedure, combined with testing and CO₂ inhalation.

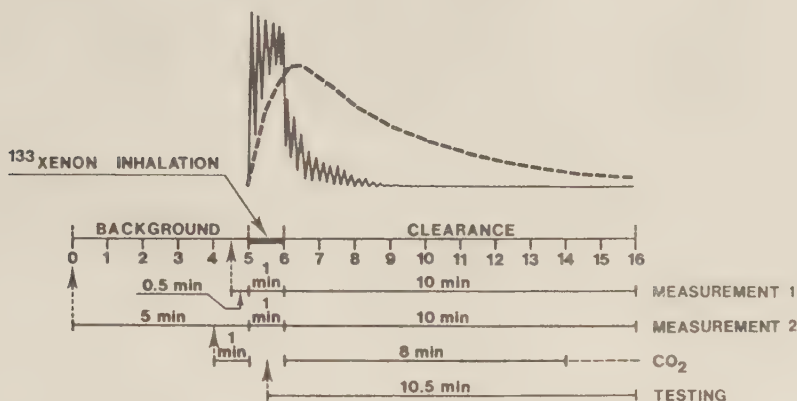


FIGURE 1. The measurement procedure differences between first and subsequent sessions (e.g. measurement 2) during rest and mental activation (testing). CO₂ was identically administered during rest and test measurements. The smooth, dotted line represents an extracranially recorded head curve while the sharply oscillating line shows a typical air curve, highest during the one minute ¹³³Xe inhalation. End tidal points, used for estimating arterial concentration of ¹³³Xe are on the trough during inhalation and on the peak afterwards.

tors, etc.) for 5 min preceding the first measurement in an attempt to eliminate any anxiety. Each measurement was made only when the subject showed normal breathing as monitored by the capnograph. During the resting measurements (normal air breathing: R; and CO₂ inhalation: RCO₂), the subjects were asked to relax with eyes closed and covered. The mental activation (subsequently labelled A and ACO₂) consisted of parallel versions of Ravens' Advanced Progressive Matrices which were presented via a slide projector on a screen suspended on the ceiling over the subject's head. This particular test was chosen because previous experience^{1, 16} showing a well-defined posterior activation of cerebral blood flow during the activation session. The testing began 30 sec after the start of ¹³³Xe inhalation (fig. 1) and was continued for the duration of the measurement. An answer (a number between 1-8) given orally via a microphone mounted in the face mask was immediately followed by a new slide which was projected for as long as the subject required.

Statistical Analysis

The main statistical methods were one-way analysis of variance, Pearson correlations and *t*-tests for related samples, constructed and programmed by one of the authors (I.P.) for a Hewlett-Packard 9825-A. All analyses were run for each variable (detector or hemispheric mean) across R, RCO₂, A and ACO₂ measurements with a simple mixed effects model.

Results

A summary of the data for each of the 32 detectors, hemispheric mean (*f*₁ and ISI) and average PCO₂ level

for the 4 measurements is given in the table. Detector localization is depicted in figure 2.

Resting Measurements

The resting flow landscape characterized by higher frontal and lower postcentral flows was evident during both R and RCO₂ (fig. 3). Mean PCO₂ increased significantly by 25%, mean hemispheric flow by 34%, and ISI by 14% (table; *F* = 6.743, *p* < 0.001).

The only significant difference in flow distribution between normo- and hypercapnia was located in a midrolandic region of both hemispheres (area 7; *F* = 2.867, *p* < 0.05). Inhalation of 6% CO₂ resulted



FIGURE 2. Average localization of homologous detectors over the cerebral hemisphere. Detectors are referred to by number.

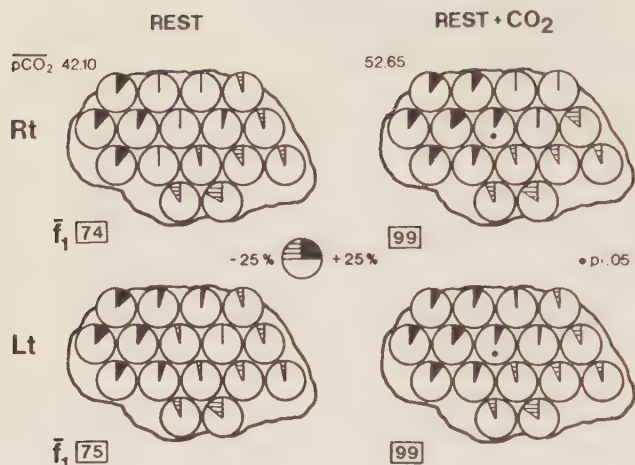


FIGURE 3. Resting flow distribution during normo- and hypercapnia. The clock symbols within each hemisphere are related to the hemispheric mean in the box. Variations to the right from 12 o'clock (black shadowing) denote flow values above, while variations to the left (striped field) represent value below the hemispheric mean. Note that the hyperperfusion during RCO_2 has not altered the resting landscape.

in significant flow increases in all cortical regions ($F = 6.743$, $p < 0.001$). Flow values as a function of PCO_2 are shown in figure 4. The CBF increases during hypercapnia were uniform among the subjects. Average breathing rate per min was $11.8 (\pm 2.44)$ and $12.5 (\pm 3.37)$ during normo- and hypercapnia respectively.

Mental Activation Measurements

Differences in rCBF between resting and problem solving consisted of significant posterior flow increases in the right hemisphere in areas 12 ($F = 4.377$, $p < 0.01$), 14, 16 ($F = 6.743$, $p < 0.001$) and in the left hemisphere in areas 14 ($F = 6.743$, $p < 0.001$), 15

($F = 2.867$, $p < 0.05$) and 16 ($F = 6.743$, $p < 0.001$). As can be seen in figure 5 there is no marked right-left asymmetry in response to mental activation. Hypercapnia did not change the posterior cerebral blood flow increases during problem solving. These are in the right hemisphere in areas 13 ($F = 4.377$, $p < 0.01$), 14 ($F = 2.867$, $p < 0.05$), 15, 16 ($F = 6.743$, $p < 0.001$), and in the left hemisphere in 14 ($F = 4.377$, $p < 0.01$) and 15, 16 ($F = 6.743$, $p < 0.001$). Mean hemispheric increases were approximately 7% and 4% in A and ACO_2 respectively. Test performance (number of correct items divided by the total number of items presented) was 64% during A and 52% during ACO_2 .

THE CO_2 RESPONSE

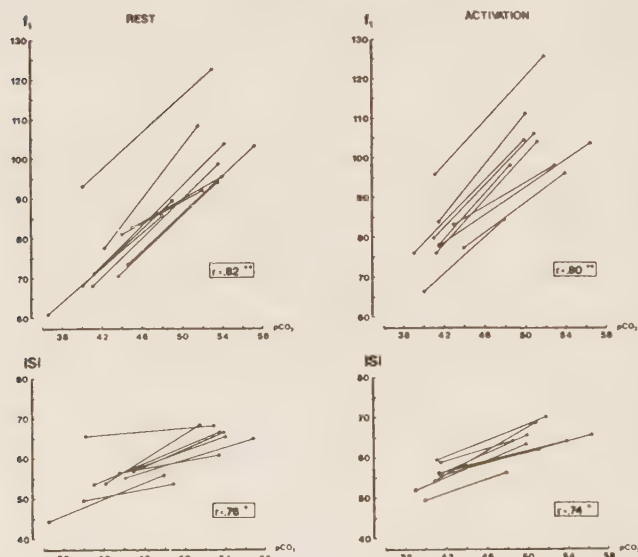


FIGURE 4. The CBF reactivity to 6% CO_2 . Flow is on the ordinate and CO_2 level on the abscissa. Note the larger response of f_1 and the inter-individual consistency. Product moment correlations between flow and CO_2 increases are shown with their significance level.

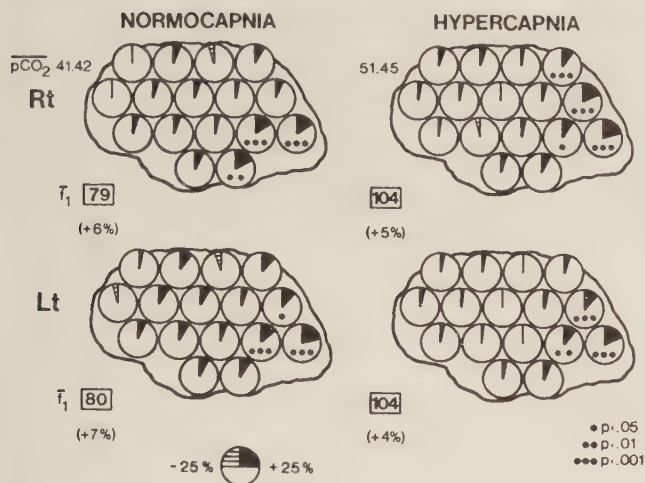


FIGURE 5. Differences from rest to mental activation. The number in the box is the hemispheric mean during the testing session while the number in the brackets shows mean increases from rest. Deviations from 12 o'clock in the clock symbols denote % increases or decreases in ml/100g/min from the resting sessions.

Discussion

The activation response to problem solving, consisting of significant posterior cerebral blood flow increases,¹ has been replicated. No significant frontal increases were observed during activation or activation and CO_2 , confirming earlier observations about the lack of specific frontal involvement in visual-spatial problem solving. The results suggest that Raven's Matrices may be clinically useful for determination of post central cerebral dysfunction.

The hemodynamic response to activation showed no hemispheric asymmetry (fig. 5). Task components known to be lateralized are visual-spatial relationships (right hemisphere) and analytical (verbal) solutions of problems (left hemisphere).¹⁷ It is thus likely that both hemispheres are involved to an equal extent in this complex task. The magnitude of activation response in flow units was shown to be fairly constant among highly variable resting flow levels: testing increased mean flows (f_1) by 4.8 and 4.0 ml/100g/min in normo- and hypercapnia. This additive effect of hypercapnic vasodilation and mental activation indicates that the activation response within an individual — and probably also among individuals — can be compared with different resting flow levels. The validity of this reasoning holds as long as the flow differences are mainly caused by arterial PCO_2 differences or other predominantly vasoactive agents, and not because of differences in metabolic rates. In an earlier publication¹ we suggested that task performance in healthy brain tissue is associated with a typical flow level, and, consequently, CBF increases during testing will be inversely related to resting flow levels when they reflect different metabolic states. The present results show that the magnitude of flow increases (in absolute units) is constant across different resting levels when these differences are vascular in origin. The CBF reactivity to arterial PCO_2 changes showed, as expected, no significant regional differ-

ences. A PCO_2 increase of 10.55 mm Hg caused an f_1 increase of 34% (25 ml/100g/min) during rest, i.e. a correction factor of 3.2% or 2.3 ml/mm Hg, which compared with what has been reported by other groups.^{7, 13} During activation the correction factors were slightly lower: 2.9% and 2.3 ml/mm Hg. The corresponding corrections for ISI were considerably lower: 1.4% or 0.75 ml during rest and 1.3% or 0.75 during activation, demonstrating the limited sensitivity of this flow parameter in hyperemic situations. The difference between our rest and activation studies is in flow levels, and this creates different correction factors by percent but not by flow. To support this point, we have checked the inter-individual variance of correction factors during rest. For both f_1 and ISI, variance of percent corrections is more than twice as high as the variance of correction by ml/100 g/min. We suggest, thus, that the vasodilatory effect of PCO_2 is not dependent on baseline flow levels (at least within the range studied here), and, therefore, corrections should be made by flow units and not percentages.

The most important finding in the present study was that hypercapnia, while causing a large global CBF increase, did not affect the mental activation flow response. The fact that the comparatively small regional flow changes during testing are clearly detectable on top of the pronounced hyperemia induced by hypercapnia is a further evidence of the reliability of our rCBF technique. rCBF changes caused by mental work were very similar during normo- and hypercapnia (fig. 5). This was confirmed by a 1-way-ANOVA comparing the differences in increases from rest to test during normo- and hypercapnia, resulting in a difference only in area 15 of the right hemisphere. The similarity of the activation responses suggests that hypercapnic and metabolic flow increases do not interact but are additive (at least in the PCO_2 range of 35 to 55 mm Hg).

The present findings raise the question of what causes the local hemodynamic response to mental

TABLE Averaged Group Values: Flows and PCO_2

	f_1				ISI			
	REST		ACTIVATION		REST		ACTIVATION	
			$+ CO_2$				$+ CO_2$	
PCO_2	42.10	2.6	41.42	1.4	52.65	2.7	51.45	2.6
Det.								
R 1	83.2	11.8	83.5	10.4	109.8	14.7	112.1	15.7
2	81.6	15.9	81.8	11.1	108.4	13.0	112.4	12.0
3	83.5	11.0	87.6	13.0	110.8	17.9	112.3	14.6
4	82.9	9.5	86.0	10.7	115.9	16.0	116.5	15.0
5	75.5	12.3	79.2	10.2	107.6	13.4	111.1	15.3
6	75.2	14.3	76.9	12.6	104.0	15.3	101.0	12.9
7	74.7	10.2	78.2	10.5	106.8	14.2	105.5	14.5
8	67.9	10.3	72.8	6.7	89.2	13.4	89.9	6.8
9	75.0	9.0	72.4	10.0	98.4	13.0	100.6	14.4
10	72.2	8.4	74.0	6.4	94.7	13.1	96.8	12.0
11	76.0	6.7	77.8	10.4	101.2	15.4	102.3	10.9
12	62.4	11.1	72.7	7.5	82.5	12.0	87.0	10.7
13	71.3	12.2	75.8	9.1	94.3	8.8	104.4	17.2
14	66.0	10.3	76.2	5.7	89.4	10.1	96.6	9.3
15	71.1	11.5	75.3	9.2	85.3	9.7	100.8	9.1
16	73.0	13.7	83.9	8.3	91.9	8.4	112.3	9.2
L 1	84.2	12.4	83.6	10.8	108.6	10.0	111.2	16.2
2	83.8	8.0	85.2	9.3	106.4	13.9	110.0	15.4
3	82.3	11.1	88.3	10.6	108.8	14.4	111.5	13.1
4	80.8	11.2	87.9	13.6	112.4	14.1	113.0	14.1
5	76.3	9.7	84.0	10.3	106.1	12.8	107.9	13.6
6	76.9	15.3	82.2	9.2	102.5	12.4	102.7	14.1
7	73.5	11.7	79.6	9.3	105.5	13.7	104.1	16.1
8	69.6	10.1	75.4	9.9	91.0	11.5	92.5	10.8
9	76.5	17.2	74.2	11.7	98.0	12.2	96.6	13.6
10	72.3	10.5	76.2	10.7	96.7	13.0	97.0	10.2
11	74.3	10.0	77.1	9.7	101.0	12.4	104.0	10.8
12	64.2	10.7	69.1	7.5	84.0	11.3	88.6	7.8
13	70.7	9.9	78.7	12.9	93.6	15.4	97.1	11.0
14	69.2	9.6	78.0	6.3	89.9	8.1	98.3	9.8
15	71.2	11.9	79.1	6.3	89.6	10.0	100.5	12.8
16	73.3	11.3	88.1	6.3	93.6	10.5	109.9	10.9
MR	74.41	9.7	78.54	7.8	99.4	11.8	103.84	10.9
ML	74.97	8.9	80.45	7.8	99.20	10.1	102.86	10.4

For each measurement the f_1 and ISI group means are given for each detector location followed by their respective standard deviations. R denotes right-hemispheric detectors (1-16) and L the homologous areas of the left hemisphere. MR and ML indicate the right and left hemispheric means. PCO_2 values are in mm Hg

work. In addition to producing hyperemia, hypercapnia also increases the arterial PO_2 level.¹⁸ It is thus highly unlikely that activation-induced flow increases during hypercapnia are caused by any chemical changes related to lack of metabolic substrates. Animal studies have demonstrated a poor coupling between CBF and tissue pH where it was shown that during bicuculline-induced seizures, net tissue acidosis did not occur until well after maximal vasodilation.^{6, 19} This would suggest that the local effects of elevated H^+ concentrations are not the immediate precursor of augmented CBF. The rise of cerebral perfusion through local vasodilation seems to occur automatically and obligatorily in parallel with increased neural metabolism and is mediated by yet unknown chemical agents and/or neurogenic control.

Acknowledgment

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FOURIER ANALYSIS OF ^{133}Xe INHALATION CURVES:
THEORY AND IMPLEMENTATION

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The ^{133}Xe inhalation method, first introduced by Mallet and Veall (1965) and later modified by Obrist et al. (1975), has been widely accepted as giving reasonably reliable and repeatable estimations of the grey matter compartment blood flow. The procedure involves extracranial monitoring of one minute ^{133}Xe inhalation and 10 minutes clearance. The mathematical analysis, as developed by Obrist et al. (1975), is based on a bicompartamental model, with a proper correction for recirculation. This model has proven valid using both artificially generated curves and clinical data.

Recordings of radiation from inferior frontal, temporal and occipital regions during ^{133}Xe inhalation are unavoidably contaminated by radiation from the air passages. This contamination actually contains two components. The first involves radiation picked up directly from the air passages. It is found in those detectors directly facing such air passages as the face mask or sinus cavities. The radiation picked up in this way contains the entire Xe energy spectrum and is quite powerful compared to the strength of the usable signal. The second component of this contamination is the so-called "scattered radiation artifact". This artifact contains relatively low energies characteristic of the Compton scatter. Its influence on the measurements can be dealt with in some degree by using discriminator windows covering only the high energy peak (81 keV) of ^{133}Xe . The two types of contamination are commonly referred to collectively as the "air-passages artifact".

Until recently, the influence of this two component artifact has been reduced by the use of a delayed start-fit-time (SFT) (Obrist et al., 1975) often combined with a mathematical correction routine (Risberg 1980). A byproduct of the delayed SFT is a reduced sensitivity to the lung-to-brain delay between the monitored end-tidal air curve and the head curves. The main disadvantage of this method, however, is the omission of the first 90 to 120 seconds of the curve which contains information about the flow of the fast clearing grey matter. Full information about the fast flows is of crucial importance in studies of the activated cortex. To overcome this drawback of the delayed SFT, we developed a new method which takes account of the air-passages artifact without losing pertinent fast-flow information.

METHOD

The clearance curve is treated as a sum of a biexponential curve (convoluted with the end-tidal air curve), the air-passages artifact and Poisson-distributed noise (Figure 1). The shape of the artifact curve is assumed to be identical to that of the averaged air curve, and its size is computed to obtain an optimal fit to the head curve, with the SFT being set at the beginning of ^{133}Xe inhalation. The observed clearance curve is expressed as:

$$N(t) = B(t) * A_{\text{end}}(t) + P_a \cdot A_{\text{ave}}(t) + N \quad (\text{eq. 1})$$

Where $N(t)$ is observed head curve, $B(t)$ is $p_1 \cdot \exp(-k_1 t) + p_2$

$\exp(-k_2 t)$, convoluted with $A_{\text{end}}(t)$ = end-tidal air curve:
 P_a is weighting coefficient of the artifact: A_{ave} is average air curve and N is noise.

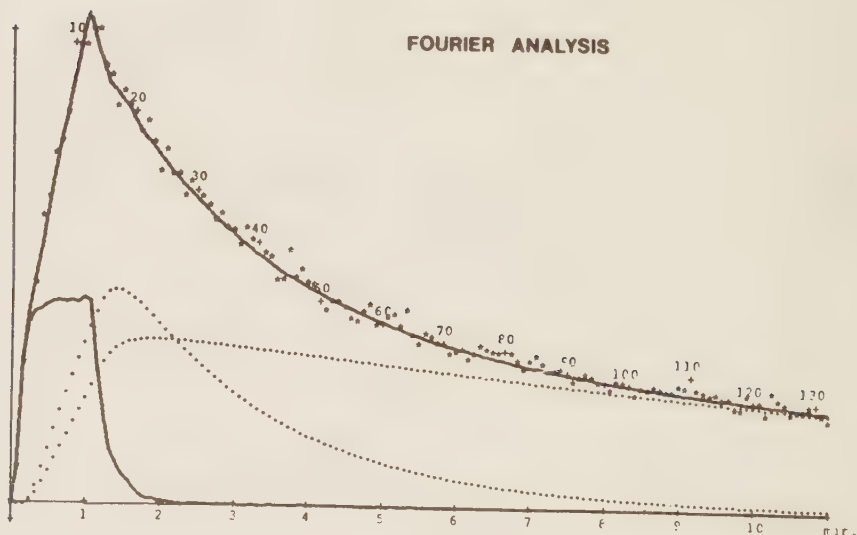
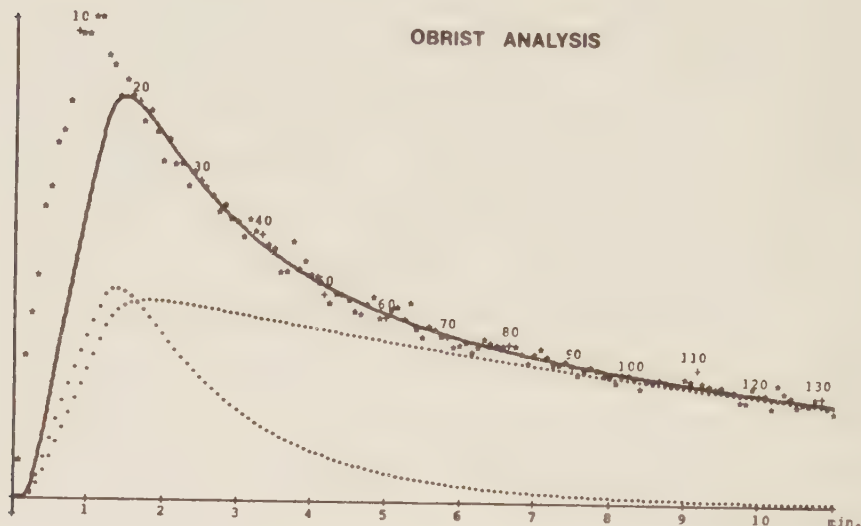


Figure 1. Two solutions for a clearance curve derived from a right-sided fronto-orbital region of a psychiatric patient, Obrist analysis above and Fourier below. Observed count rates during 11 minutes are shown as asterisks, the two reconstructed flow components (convoluted with the end-tidal air curve) as dots, and the full reconstructed function as a continuous black line. The Fourier solution shows also the air passage artifact as a continuous line.

The analysis begins with conversion of all head and air curves to the frequency domain by a Discrete Fourier Transformation (DFT). A standard method for calculating the DFT is used, according to the formula:

$$F(X(m)) = \sum_{n=0}^{N-1} X(n) e^{-j(2\pi/N)nm} \quad (\text{eq. 2})$$

Where $X(m)$ is the function in the time domain, $F(X(m))$ is its Fourier transform, representing the amplitude and phase of the sinusoid at frequency $\omega_k = 2\pi m / NT$ (eq. 3), N is the number of intervals in the time domain and T the length of the intervals (in minutes). For the biexponential analysis, only five samples ($m=0$ to 4) of the frequency spectrum are actually calculated. The lowest sample ($m=0$) corresponds to the part of the signal which either does not change (in time) at all (noise due to contamination of the detectors or the electronic noise of photomultipliers), or else changes very slowly (with a time constant larger than the clearance time - 10 min as standard). The highest frequency sample ($m=4$) corresponds to a k_1 value (see legend to equation 1) of approximately 2.4 - well above the fastest grey matter flow expected.

After the Fourier transform of all three curves are obtained, a deconvolution is performed by dividing, point by point, the frequency spectrum of the head curve by that of the end-tidal air curve. Since the spectra are complex, having real and imaginary parts, a complex division routine is used. Five complex values are thereby obtained, characterizing the transfer function of the brain tissue. At this

point any standard technique of curve fitting (or more correctly "data fitting") can be employed to find a set of parameters k_1 , k_2 , p_1 , p_2 , and p_a which give, after a convolution and a Fourier transformation, five complex values as close as possible to those obtained from the analysed curves. We decided to use the classical least-sum-of-squared-errors method. A set of five normal equations is created and then solved using a high precision algorithm (Carnahan, B., et al., 1969). This method has the advantage of a rapid convergence (the results are typically obtained after 3-4 iterations), provided that good estimate of the starting values are given. A good initial estimate of the size of the air-passages artifact is especially important.

Our method has given very rapid and accurate results in 98-99% of all cases. In the remaining 1-2%, the estimation of starting values is not good enough (most often due to excessive noise), causing a divergence. In such cases a monoexponential analysis is attempted. A monoexponential solution will be obtained if either the curve was truly monoexponential (allowing for $p_2 \neq 0$) or if the signal/noise ratio was not good enough to provide the necessary information for a biexponential solution. The authors are currently working on improving immunity to divergence caused by noise.

The algorithm described above has been implemented on the Hewlett-Packard 9845 and 9825 desktop computers.

RESULTS

Compared to the classical Obrist program, the new analysis is about 6 times faster. It should be mentioned that a 5-parameter analysis could be implemented in the time domain as well, but the calculation time would be much longer than is the case for the Obrist program.

In order to "dry run" the program, the method of generating artificial curves used by Obrist et al. was employed, thus assuring the same conditions of comparisons. A large number of artificial curves with noise were created in order to establish mean values and standard deviations of the results. Five groups of curves were generated: Normal flow ($k_1=1$), slow flows ($k_1=0.5$ and $k_1=0.7$), and high flows ($k_1=2$ and $k_1=1.5$). Values of $k_1=0.5$ and $k_1=2$ are rather unrealistic, but they were employed to test the program's ability to cope with extreme conditions. In each group three curves were generated: One without an air-passages artifact, one with an artifact contributing 20% of the count rate at the peak of the clearance curve, and one with a 50% air-passages artifact contribution. Each of these curves was analysed 200 times, varying the superimposed noise. Analysis was performed using the new technique as well as with the traditional one. The above procedure was repeated 6 times for 6 different values of the count rate, ranging from 100 counts/second to 1000 counts/second. The total number of curves analysed was 18 000.

The results show near total immunity to the air-passages artifact. No statistically significant difference could be found between the mean values of k_1 for the curves with and the curves without an air-passages artifact. The observed increase in SD in curves with the artifact corresponded exactly to the additional noise inherent in the increased count rate. The mean k_1 was never further than 0.1% from the expected value, and the SD's were significantly lower using the new program. For conditions commonly encountered in practice (600 counts/second, normal flow, 20% air-passages artifact) the SD of the k_1 was 3.08% using the new program compared to 5.53% using the old one. Considerably larger differences were observed for the very slow and very fast curves with low count rates. For the curves having $k_1=0.5$ and count rates of 100c/s, the SD of the new method was 9.1% compared to 20.1% for the old. The new method apparently copes much more adequately with extreme conditions; the old program often merely printed out error messages, being unable to fulfill the convergence conditions.

Sensitivity to the time delay between the end-tidal air curve and head curves was also tested. It was found to be in the range of 1.2% per second for k_1 (a standard correction for the 5-second delay is performed prior to all calculations). The reason for such a low value is that the time shift affects the Fourier spectrum in a way almost identical to the air-passages artifact. The correction for the air-passages artifact therefore also takes the time delay into account. Although the obtained values of the

size of the air-passages artifact are offset by the time delay, the other parameters (k_1 , k_2 , p_1 , p_2) are not affected by either. Consequently, a negative value for the air-passages artifact may occasionally result. Such values merely imply that the air-passages artifact was 0, or very close to 0, and that a significant time shift was recognized and taken into account.

On the basis of the investigations using artificial curves, we conclude that the new program seems to resolve the air-passages artifact problem and give correct results as far as the model on which the old technique is based is correct. Whether or not this model has omitted some artifact capable of negatively influencing the program could only be determined performing clinical tests. Such tests were also necessary to find out whether the new method would give not only results less influenced by noise, but also supply more information about the very fast compartments. For a description of these clinical investigations please refer to Prohovnik et al. "Fourier Analysis of ^{133}Xe Inhalation Curves: Preliminary Empirical Validation", included in this publication.

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FOURIER ANALYSIS OF ^{133}Xe INHALATION CURVES:
PRELIMINARY EMPIRICAL VALIDATION

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The theory and method of Fourier analysis of Xe-inhalation curves are described in the preceding paper (Jablonski, et al., this volume). On computer-simulated curves this new analysis has been shown to be more accurate and reliable, as well as faster, than the conventional analysis (Obrist, et al., 1975). The main advantage of Fourier analysis seems to be the effective isolation of irrelevant radiation counts which are added to cerebral clearance curves from the air passages and sinuses of the face and throat. This radiation, termed "Air-Passage Artifact" (APA), prevents the conventional analysis from using the early part of cerebral clearance curves.

Success in solving computer simulated curves is, however, very much dependent on the assumptions of the model. Ultimately, the only validation of mathematical solutions can be against the physiological reality with its constraints, artifacts and associated unknowns. This report describes results of Fourier analysis of clearance curves obtained from normal subjects, as well as psychiatric and neurological patients.

We checked, first, whether Fourier analysis (FA) yields a better correspondence between the observed and fitted curves than the conventional analysis (CA). The main period of interest was the first 200 seconds, where much crucial information about fast flows is hidden by the APA. Secondly, to further check the validity of fit, we chose to compare flows at normal baseline conditions ("rest"), computed by FA and CA. This normal pattern is a good criterion since

it is well-known and easily replicated. Finally, theoretical considerations indicated that FA should be especially advantageous in hyperemic conditions. We checked this in normal subjects who were "activated" by psychological test procedures. The definition of local and global hemodynamic responses is of major interest since, in addition to its research potential, it is of considerable clinical value. We also compared FA to CA results in patients, some of whom were expected to have focal hyperemia due to epileptic activity.

METHOD

All rCBF measurements were made with one-minute inhalation of the tracer, followed by 10 minutes of clearance using a bilateral, 32-detector standard system (NOVO Diagnostic Systems, Hadsund, Denmark). Data were analysed by the conventional analysis (Obrist, et al., 1975 and Risberg, 1980) and by Fourier analysis (Jablonski, et al., 1979). In addition to two-compartmental parameters we have computed the Initial Slope Index (ISI, Risberg, et al., 1975) between the second and third minute with CA and between 30 to 90 seconds with FA.

RESULTS

Fourier analysis does, indeed, succeed in isolating the APA. This was indicated by visual examination of curve fitting (e.g. fig. 1, Jablonski, et al., this volume)

and by goodness-of-fit tests, described later. As an illustration, we have computed APA magnitude for each of our 16 cortical regions on a random sample of 22 measurements. The results are shown in fig. 1, expressed as the ratio (percent) of APA counts to total curve counts at the peak of the curve.

Distribution of Air-Passage-Artifact

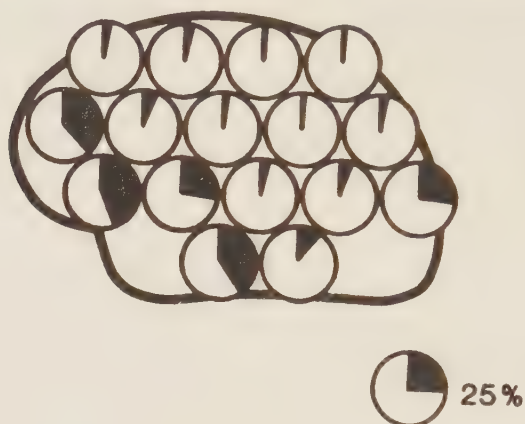


Figure 1. Ratio (percent) of APA-derived counts to total curve counts at the peak of the cerebral clearance curve. Typical small sample ($n=5$) of FA-defined APA; right and left detectors averaged.

The topographical distribution is in very good agreement with the results obtained from conventional APA correction (Risberg, 1980), but the magnitudes revealed by FA are much larger. The APA distribution is very stable and consistent; regions with largest contamination will later be referred to as APA areas.

GOODNESS OF FIT

In addition to visual examination of observed and fitted curves, we have conducted a formal, statistical analysis, consisting of four experimental parameters. For this analysis, the FA-defined APA was subtracted from the observed curve and was not added to the reconstructed curve. The comparison is, thus, between two pure cerebral curves but the Poisson-distributed noise associated with the artifact still exists in the observed curve. This goodness-of-fit analysis has been carried out on about 2 500 curves, for both CA and FA. The results of statistical testing are very highly significant (usually far beyond the .001 significance level with a one-way ANOVA), making a larger sample unnecessary.

The first experimental parameter was Curve Fit SD (CFSD): a measure of goodness-of-fit that describes the standard deviation of the differences between the observed and fitted curves, independently of count-rate (ideal value: 1; Risberg, 1980). We computed this parameter twice for each analysis: once from 20 seconds after start of Xe inhalation and once from SFT (Start-Fit-Time, established by the usual Obrist criterion). Beginning at SFT, CA was shown to be slightly superior, the difference in CFSD commonly being less than 0.1 and reaching statistical significance ($p < .05$) only in APA areas. When CFSD was computed over the whole curve, FA was found to be very superior: FA had values between 1 and 2, whereas CA showed values in the range 2 to 11. Differences were very highly significant and clearly related to the typical levels of APA in each area.

The other three parameters were based on calculations of deviant points. These are defined as differences between the observed and fitted curves which are larger than three times the square root of the observed count-rate. Since this square root is equal to the standard deviation of the radiation scatter, these differences are significant at about the 1% level. The number of deviant points was very significantly higher with CA than with FA. The magnitude of their average deviation ranged 20-200 cps with CA, and -20 to zero cps with FA; extreme values were always seen in APA areas. Finally, the location of these deviations was earlier, and more constant, with CA than with FA. To summarize: FA drastically reduces the number of misfitted points, and the average magnitude of misfit. Fitting mistakes with CA, as expected, are concentrated near the end of the inhalation period while they are more widespread with FA. A slight advantage in fitting for CA was found for the later part of the curve (approximately after 200 seconds).

THE RESTING PATTERN

Both CA and FA were performed on 21 resting measurements in 19 healthy young subjects. Results will be reported for the bicompartmental parameters (f_g , w_g , k_2) and for ISI, which was computed on the period 120-180 sec with CA and 30-90 sec with FA. In an attempt to separate global from local effects, results will be reported in terms of mean hemispheric flows and regional distribution values, i.e., regional flows expressed as percentage of mean hemispheric

flows.

All changes of mean hemispheric bicompartmental parameters were extremely small (within 1%) and nonsignificant. ISI was significantly increased by about 14% due to its earlier period of calculation with FA. Variance of mean hemispheric values was nonsignificantly higher with FA for all parameters.

We found relatively large effects regionally, mostly in APA areas. All three flow indices (fg , k_2 , ISI) were remarkably increased in the occipital pole (10-16% in distribution values) and decreased in our two prefrontal detectors, especially in the left side (2-10% on the right, 5-13% on the left). In addition, less radically, flow distribution was increased all along the ventral periphery (especially k_2 in posterior areas, fg and ISI in anterior, APA areas) and decreased along the upper periphery. Variance of regional flows was generally slightly higher with FA, but variance of distribution values was lower, for fg and ISI. The general factor of flow is, thus, more variable with FA but the relative regional pattern seems more stable. Changes of wg were extremely small, mostly increases parietally and decreases along the anterior and ventral periphery.

NORMAL AND PATHOLOGICAL HIGH FLOWS

Normal data are taken from two projects currently active in our laboratory. Table 1 shows results from the complete series: activation responses (% increases of fg) with FA and CA are compared during three visual stimulation conditions in normal subjects.

Table 1. Occipital and mean hemispheric activation responses to three visual stimuli. Activation responses are denoted in percent and refer to fg.

	CA		FA	
	occipital	hemispheric	occipital	hemispheric
stationary spiral	6	0.5	7	2
rotating spiral	7	3	12	6.5
SAE test	3.5	2	8.5	9

The superiority of FA is evident for all three conditions. We have also collected data from an ongoing study involving auditory-verbal stimulation of normals. The results show 4% increases of hemispheric mean flows with FA and none with CA. Local flow increases in posterior-temporal regions average 9% with FA and 6% with CA.

The logical next step and the ultimate criterion was testing FA in pathological cases. This was also the most difficult stage, due to the lack of clear criteria of diagnostic success. We have, by now, analyzed about 60 measurements and have not yet found a single case in which CA shows a clear diagnostic superiority compared to FA. Several cases have, however, been studied with diagnostic superiority of FA.

During EEG-verified epileptic seizures,
provoked by hyperventilation.

468 T.C.
♂ 30 y

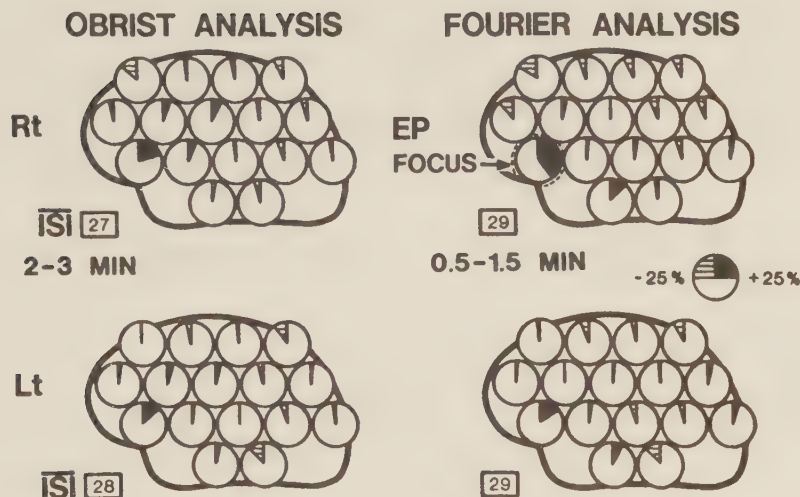


Figure 2. A patient during EEG-verified epileptic seizures, provoked by hyperventilation. Numbers in boxes indicate hemispheric mean flows; clock symbols show percent deviation from the mean flow (black=above mean, striped=below mean). Note the focal asymmetry with FA.

468 T.C.
♂ 30 y

15 minutes post-ictally.

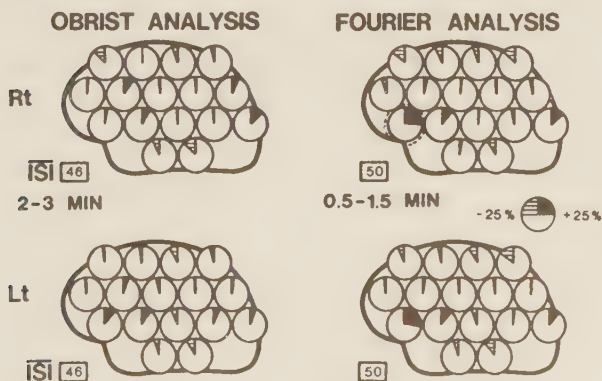


Figure 3. Same patient as fig. 2, 15 minutes postictally. Note the higher focal flow with FA. Symbols as in fig. 1.

RIGHT TEMPORAL LOBE EPILEPSY

625 SM
♂ 26 y

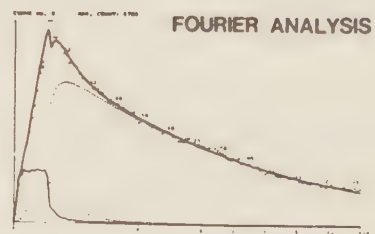
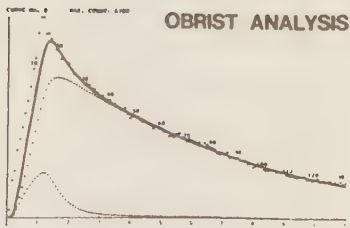


Figure 4. A case of right temporal-lobe epilepsy. Symbols as in previous figures, and the reconstructed and observed curves are shown underneath. Both analyses showed a very small fast compartment in the focus area, but only FA detected the hyperemia in this small tissue volume. Note the APA and the better fit with FA.

Right Hemisphere Epileptic Activity:

REGIONAL FLOW ASYMMETRIES

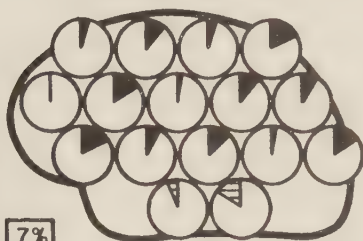
474 K.T.

♂ 37y

OBRIST
ANALYSIS

ISI 7%

2-3 MIN



- 25 % + 25 %

FOURIER
ANALYSIS

ISI 11%

0.5-1.5 MIN

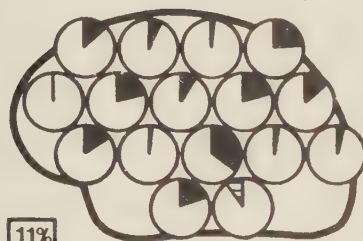


Figure 5. A case of right hemisphere multi-focal epilepsy, lesions verified by CT-scan. Numbers in boxes show asymmetry of mean hemispheric flows, clock symbols show regional flow asymmetries, all expressed as right flow divided by left flow (percent). Note the sharper asymmetry by FA, and the reversal of asymmetry in the anterior temporal area.

The clearest examples are shown in figures 2-6.

In most of the cases validating support for the diagnosis is given by other methods such as EEG or CT-scan. In several other cases we cannot as yet prove FA superiority due to lack of supporting evidence.

A26 U.I.
 ♀ 73 y

Percent increases of flow
 from rest to test.

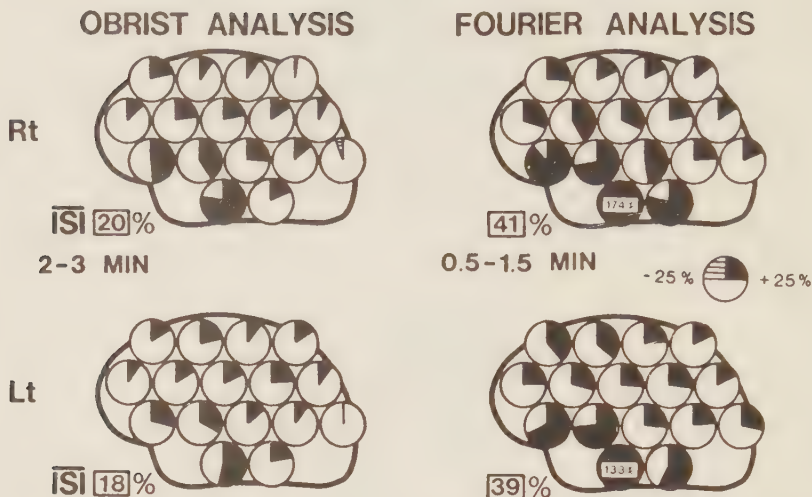


Figure 6. A case of suspected presenile dementia. Numbers in boxes show activation response of mean hemispheric flows, clock symbols denote regional activation; all refer to percent increases of fast flow from rest to testing. The test used is very difficult, and involves verbal memorization with a strong component of selective attention.

We have concentrated on hyperemic pathologies (mostly patients with focal epilepsy) because we expected the largest FA advantages there. We have, however, also analyzed cases with ischemia where extremely low flows are often associated with extremely low count rates. In these cases, as well as in other technically unsatisfactory measurements (leaks, movement artifacts, etc.) we have found consistently higher tolerance for artifacts by CA. Technically bad measurements might still yield clinically useful data with CA, while FA failed to converge or yielded obviously unrealistic results.

COMMENT

Fourier analysis does, indeed, fulfil its theoretical promises. It utilizes the information contained in the early part of the curve after isolating the air-passage artifact, and it is therefore more sensitive to high flow rates. It is thus more effective in defining activation responses and hyperemic pathologies. At low or intermediate flow rates (and technically good measurements with small APA) it seems to yield results identical to CA. If the APA is very large, however, FA is superior to CA even with low flows. On the other hand, FA seems more sensitive to violation of the assumptions underlying the physiological model of CBF. It is less tolerant than CA of flows that are not strictly bi-compartmental (such as in the occipital poles), and it sets higher demands on the technical qualities of the measurement (e.g. with regard to leaks and movement artifacts). Further computational improvements are currently being tested, and we expect Fourier analysis to become a highly reliable and sensitive method for solution of rCBF inhalation curves.

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PAPER IV.

OBSERVATIONS ON THE FUNCTIONAL SIGNIFICANCE OF REGIONAL CEREBRAL BLOOD FLOW IN "RESTING" NORMAL SUBJECTS

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Abstract—Regional Cerebral Blood Flow (rCBF) of 16 cortical regions was measured bilaterally in 22 healthy adults, with 4–8 repeated measurements per individual. All measurements were done during "rest", i.e. with minimal external stimulation, by the Xe-133 inhalation method. The data are presented to serve as normal controls for research and clinical work, but more importantly because of their significance for neuropsychological theory. Some rCBF variance is shown to be meaningfully related to handedness, habituation processes, biological rhythms and possibly to regional lateral dominance. Further data and discussion relate to the possible role of frontal lobe structures during non-task-oriented cognition. Finally, data are interpreted as showing that regional functional coupling across the midline, in this situation, is inversely related to the characteristic level-of-processing associated with each area.

MEASUREMENTS of regional cerebral blood flow (rCBF) provide a new way of mapping the functional organization of the human cortex. Such measurements have now been used for studies of basic sensory-motor and speech functions [1–7] as well as verbal and spatial reasoning [8–12] and memory and learning [13, 14]. The interpretation of CBF patterns as cortical activity maps is based on the fact that brain tissue regulates its own blood supply in accordance with its metabolic demands, which are determined by the amount of "work" being carried out by the tissue [15]. Measurements of the local cortical blood flow thus yield an index of the regional activity level. The present rCBF technique is a nontraumatic and safe procedure which allows more accurate localization of functions than electrophysiological methods. The reader is referred to RISBERG [16] for a recent comprehensive review of the technique and its applications.

In clinical practice, a patient's rCBF results are commonly compared to data from normal "resting" subjects. Studies of cortical organization in normals are also often done by comparing an "activation" measurement (made while the subject is performing a task) to a "resting" measurement; the resting state is usually defined as closed eyes, quiet surroundings and minimal interaction with the subject. For both clinical and research applications it is obviously important to determine the normal resting rCBF level, its regional pattern and its variation within and among individuals. One of the aims of this article is to report the results of a study which was designed to supply this information.

The main purpose, however, is to report findings of basic significance to neuropsychological theory. The variation, inter- and intra-individual, of rCBF during rest has commonly been considered noise, reflecting only measurement error. We intend to show that this is not true, that a part of this variation can be shown to consist of biologically and neuropsychologically relevant relations. Furthermore, we will present and discuss findings which

may increase our understanding of the functional organization of the human cortex and the coordination of activity in its various parts. These findings illustrate the unique potential of rCBF studies for neuropsychology.

METHODS

Subjects

The subjects were 22 young male volunteers (mean age $28 \text{ yr} \pm 7.3 \text{ yr}$), mostly students or hospital employees, who were paid about 100 Swedish Crowns each. All were right-handed, as measured by OLDFIELD's Edinburgh Handedness Inventory [17]. Their health was verified by negative answers to questions about past accidents, head trauma, headache and fainting episodes, epileptic phenomena and previous hospitalizations.

The rCBF measurements

Our measurement technique is based on inhalation, during 1 min, of a mixture of air and the inert and diffusable radioactive tracer ^{133}Xe ; Xenon inhalation is followed by 10 min of normal air breathing. The tracer diffuses into brain tissue from arterial blood, and is washed out again (after the inhalation minute) by venous blood and then cleared out through the lungs. Gamma radiation, emitted by the tracer, is continuously monitored by extracranial detectors and is a function of tracer concentration in the tissue. Changes of this concentration are related to blood flow through the tissue, e.g. the tracer disappears faster with higher blood flow. Mathematical techniques are available for reliable flow calculation from the concentration curves; for further details about theory and calculations see [16, 18, 19]. In our laboratory, gamma radiation is bilaterally recorded by 32 detectors and processed by a standard rCBF system (Medi-tronic-Novo Diagnostic Systems, Hadsund, Denmark). The data derived by the rCBF system were fed to a Varian-73 minicomputer for flow calculations according to principles developed by ÖBRIST *et al.* [18] and RISBERG *et al.* [19]. The following flow parameters were calculated:

f_g : the fast component, calculated from a biexponential analysis of the curve, representing mainly blood flow of the grey matter in normal man.

k_2 : decay constant of the slow component of the curve, representing the clearance in cerebral white matter with some contamination by extracerebral tissues.

w_g : the proportion (relative weight of tissue recorded) which is perfused by the rapid flow (f_g), expressed as percentage of total perfused tissue.

ISI: Initial Slope Index, based on the decay constant of the 2–3 minute period of the recirculation-corrected curve. This flow index is dominated by grey matter flow but is less sensitive to artifacts and noise than f_g .

Final data processing, prior to statistical analysis, included correction for remaining activity from previous measurements, correction for leaks and scattered radiation from air passages, and a careful check of curve fitting. The 16 regional flows in each hemisphere were combined to a hemispheric mean flow. Each regional flow is expressed as a percentage of the hemispheric mean flow, and is referred to as distribution flow.

Detector placement

The detectors were placed in parallel in two holders positioned at a right angle to the left and right lateral surfaces of the subject's head. As indicated in Fig. 1, the same three detector pairs (9R-9L, 7R-7L, 6R-6L) were always placed approximately over the Rolandic fissure by a procedure based on data from MONRAD-KROHN and REFSUM [20]. The distance on the vertex was measured from nasion toinion; a point one centimeter behind the midpoint of that distance was taken to be the junction of the Rolandic fissure with the midline. The fissure was then assumed to extend in an anterior-ventral direction for a distance of 10 cm, forming a 23° angle with the transverse plane. The same three detector pairs were always placed on this presumed fissure (Fig. 1) and therefore the whole detector block had the same relationship to the other parts of the brain, with unavoidable variations due to inter-individual anatomical differences. After the first measurement a Polaroid picture was taken of the skull with indications of detector placement, and used for placement in consecutive measurements. Detectors will be referred to by their numbers, as in Fig. 1, with R or L to indicate right or left hemisphere.

Design and procedure

Before the first measurement all subjects received detailed explanations about the method and procedure. Each subject underwent 4–8 measurements, with inter-measurement intervals of 5 min, 2 hr or 1 week. The "resting" state was induced by covering the subject's eyes and maintaining strict silence in the laboratory. Noise levels generated by various mechanical sources (pumps etc.) did not exceed 44–46 dB(A) (measured by a Precision Sound Level Meter, Type 1613, Brüel & Kjaer, Copenhagen) and were constant.

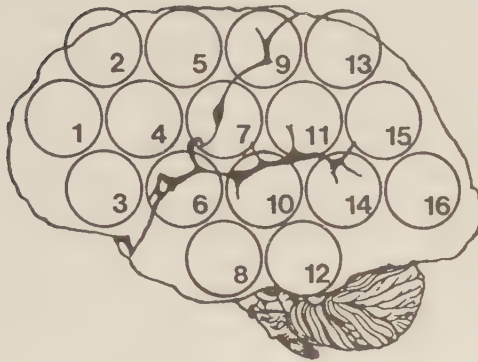


FIG. 1. Assumed average location of 16 detectors on the cortex of one hemisphere: the other hemisphere is identically covered. The Rolandic and Sylvian fissures are also shown.

RESULTS

Flow patterns

Averaged flow values for all measurements of all subjects are depicted in Fig. 2, for both f_g and ISI. Two results are immediately obvious: the two hemispheres are essentially identical, and both show flows in the frontal lobe which are 5–15% above the hemispheric mean. The central sulcus flow is close to average, and so are the parietal and occipital lobes; the temporal lobe has the lowest flows, about 5–15% below hemispheric mean. There

THE BILATERAL RESTING LANDSCAPE

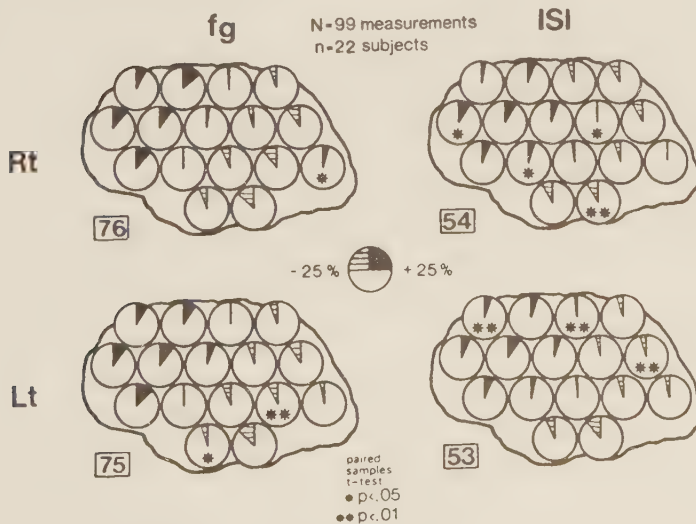


FIG. 2. Flow values averaged across all groups and all subjects. Hemispheric mean flows (f_g in ml/100 g min) are indicated in the boxes. Regional distribution flows are shown as deviations from the mean: black shadowing indicates a value higher than the mean, striped is lower than the mean. A 25% deviation from the mean is equal to 90° in the clock symbols.

are actually some significant asymmetries (by a t -test for dependent means), but they are of a very small magnitude: hemispheric means are higher on the right, and there are some regional asymmetries marked with asterisks in Fig. 2 at the location of the higher value. An additional, and expected, finding is the relative "flatness" of the ISI pattern (compared with f_g), i.e. less marked deviations from the hemispheric mean. Numerical results for the total sample (99 measurements) are shown in Table 1, together with the corresponding values of k_2 (white matter flow) and w_g (relative weight of grey tissue in each area). These latter two indices show no asymmetry in hemispheric means. There are, however, considerable local asymmetries of w_g distribution, which are arranged topologically: the anterior temporal lobe (including a fronto-orbital area) shows larger grey weight on the right side; the dorsal periphery (including the occipital pole and frontal and parietal regions near the vertex) shows higher w_g on the left side.

Variation patterns

Again, the patterns are essentially identical for both hemispheres with both flow parameters, but ISI variance is clearly lower than that of f_g (see Table 1). Generally speaking, and certainly predictable by the anatomic constraints of the method, the variance is higher at the periphery of the measurement field than in the center; the detectors at the periphery "see" less brain tissue, have a lower count rate, and thus less reliable values can be derived. Note that flow variation is higher in the left premotor and posterior-temporal areas, and higher in the right occipital pole and parietal area (by a t -test for related variances).

Relations with handedness

As mentioned, all our subjects were right-handed; the Edinburgh Handedness Inventory allows, however, quantification of handedness, and the 16 subjects for whom we had complete handedness data were spread over a range of Laterality Quotients from 60 to 100. Of these 16 subjects we took the highest third with respect to right-handedness ($LQ = 100$, $n = 5$) and the lowest ($LQ \leq 75$, $n = 5$), and ran an analysis of variance on inter-hemispheric differences (right minus left) of flows between the two groups. This procedure was adopted because a straight comparison of flows between them would be contaminated by differences in pCO_2 and other systemic effects.

The mean hemispheric flow difference (mean right minus left) was 1.84 for the high right-handedness group and -0.70 for the low ($F = 5.825$, $P < 0.025$). The corresponding ISI differences were 1.31 and -0.15 ($F = 11.036$, $P < 0.002$). In addition, Fig. 3 shows the regional differences in local lateral asymmetry (right minus left) for f_g , ISI and w_g , expressed in their actual measurement units. Significant and relatively large differences are seen in superior frontal areas (where flow asymmetries are positively related to handedness) and posterior-superior temporal and occipital areas (with a similar trend). No appreciable handedness-related differences can be seen for grey-matter weight (w_g) except in the superior parietal lobule where the asymmetries are positively related to handedness. These results were confirmed by significant product-moment correlations (between regional asymmetries and handedness score, for all 66 measurements of the available 16 subjects) at the 0.05 level for detectors 5 (positive), 8, 10 and 12 (negative). No significant correlations emerged for w_g .

To summarize: high right-handedness tends to be associated with increased right hemisphere flow, especially in the frontal lobe and some posterior areas, with apparently higher

Table 1 - Regional Distribution Values, Hemispheric Means, Standard Deviations and Significance of Lateral Asymmetries.

	fg		ISI		K2		wg	
	Left	Right	Left	Right	Left	Right	Left	Right
1	109.7	111.6	106.9	108.9★	97.1	99.6	97.1	98.1
2	111.0	108.5	106.0★★★	102.8	96.3	94.5	93.9★★★	91.9
3	113.2	109.8	105.6	106.6	94.5	96.9	90.4	93.8★★★
4	110.7	110.7	110.6	110.3	109.4	111.0	105.1	104.7
5	107.9	107.1	105.2	104.2	101.0	101.7	98.1	97.6
6	99.6	100.2	101.5	102.7★	108.7	109.4	105.2	106.2★
7	102.7	102.5	103.6	103.2	111.7	110.0	105.2	104.2
8	95.1★	92.7	92.7	92.3	95.0	95.9	92.5	94.9★★
9	99.9	99.2	99.1★	97.3	96.8	94.7	97.7★★★	95.9
10	93.1	93.4	99.1	99.4	113.2	112.6	112.1	111.4
11	95.9	96.9	98.4	99.9★	103.6	105.3	104.0	105.1
12	86.2	86.9	89.1	90.9★★★	99.4	101.7	101.6	104.1★
13	95.1	96.3	94.7	93.3	98.4	88.4	94.7★★★	91.4
14	91.7★	88.9	96.2	96.0	103.9★	100.2	106.7	110.0★★★
15	91.8	92.1	95.7★	94.3	91.2	91.2	102.0★★★	98.9
16	98.5	101.8★	97.2	98.1	89.1	88.8	93.1★★★	90.8
	11.34	13.93★	8.28	8.48	11.13	11.78	7.28	6.32
Hemispheric mean	75.03	75.66★	53.36	53.79★★★	0.12	0.12	43.22	43.34
SD	9.09	9.07	6.22	6.34	0.02	0.02	3.27	3.19

Significance of lateral asymmetry by dependent t-test: ★ p < .05 ★★ p < .01 ★★★ p < .001

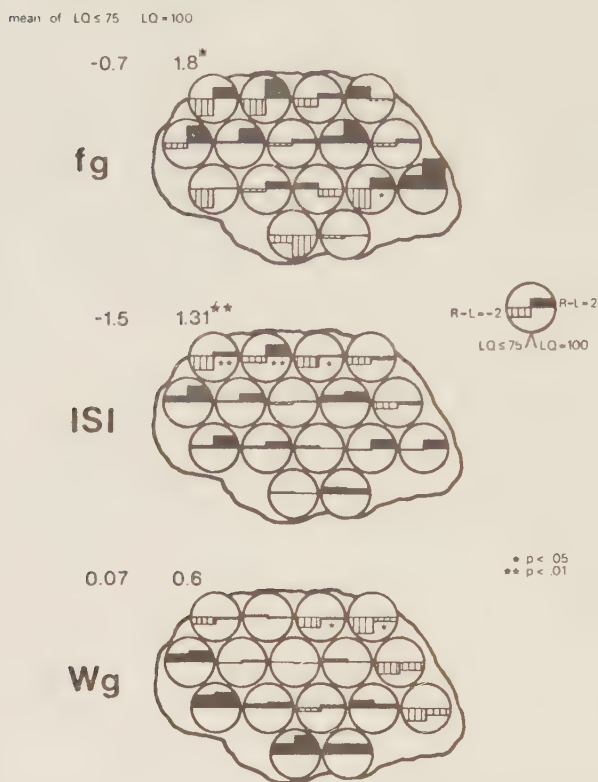
rCBF ASYMMETRIES IN HIGH AND
LOW RIGHT-HANDEDNESS

FIG. 3. Hemispheric means and regional values are here compared between 5 perfectly right-handed subjects (LQ = 100) and the five least right-handed subjects (LQ $\leq$ 75). Within each region, the right bar shows the local asymmetry (right minus left) for the high right-handedness subjects, the left bar shows the local asymmetry for the least right-handed group; a black bar denotes right > left, a striped bar means left > right. Asymmetries of hemispheric means are shown to the left of the brains, and asterisks denote significance of a one-way ANOVA.

flow in left anterior temporal regions. We could not find significant relationships of handedness with weight of grey matter.

Serial effects on rCBF

We suspected the existence of two rhythmical components in CBF and, in addition, a "first run" effect. The cyclical components correspond to the well-known circadian and ultradian rhythms, with periods of 24 hr and about 100 min, respectively. The small number of observations possible on each individual, due to radiation dose limitations, did not allow rigorous statistical testing of these hypotheses. We did, however, confirm the contribution of the two rhythmical components by visual examination of the data. A detailed description of time-related variance in rCBF will be presented elsewhere.

The "first run" effect has commonly been referred to as habituation to the measurement situation. We ran a one-way ANOVA on 16 subjects for whom we had full data, comparing

measurements 1, 2, 3 and the last one. Mean flows decreased from the first to the second measurement, non-significantly (about 7% in f_g , 4% in ISI, with a perfectly constant pCO_2) but the more striking effect was in variation. Standard deviations of f_g went down by about 50% (from 11.8 and 12.7 to 6.1 and 6.2) and of ISI by about 25% (from 8.4 and 8.3 to 6.3 and 6.2). Variance stayed low during the second and third measurements, and rose slightly at the last (up to about 8 in f_g , 7.5 in ISI). The mean flows of the third and the last measurements were intermediate for f_g , and as high as the first for ISI. Standard deviations of the difference between the hemispheric means of first and second measurements were 10.01 (R) and 9.07 (L) for f_g , 4.02 (R) and 3.58 (L) for ISI. No significant habituation trends were seen in regional flows, although there were considerable non-significant decreases of activity level in the left superior prefrontal (detector 2L, decrease of 5% in f_g and 3% in ISI) and left orbital (detector 6L, 7% in f_g and 3% in ISI) regions. The orbital decrease was maintained throughout the series, whereas the superior prefrontal level rose again after the second measurement. Habituation of variation was mainly seen in a left premotor area (detector 5L, significant decrease of 39% in f_g and 20% in ISI), but also in parietal regions (detectors 9R and 13L), these decreases being maintained throughout the series.

Inter-hemispheric regional relations

Figure 4 shows product-moment correlations between symmetrical regions in the right and left hemispheres, computed as usual on the distribution values (% of hemispheric mean). The correlation between the mean hemispheric flows is practically a unity, and correlations done on actual flows are also very high. As Fig. 4 shows, distribution value correlations are

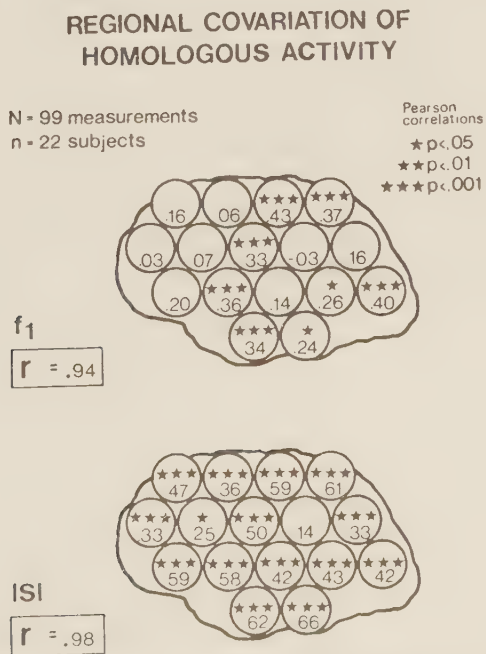


FIG. 4. Product-moment correlations between distribution flows of homologous areas in the two hemispheres. Stars denote the significance of correlations, and the boxes to the left show correlations between the mean hemispheric flows.

generally higher for ISI, due to the noise and instability inherent in f_g . No significant negative correlations were found. The ISI correlations are positive and significant in all regions except the inferior parietal area, and a central-frontal region is lowest. f_g shows significant correlations only along the Rolandic fissure (and superior-anterior parietal area), the occipital pole and some temporal areas. In LURIA's [21] functional anatomy terms, the interhemispheric coupling during rest seems highest in sensory projection areas and lowest in the tertiary association areas.

DISCUSSION

The discussion is divided into two main parts, the first being mainly concerned with the rCBF method, the other concentrating on issues of neuropsychological theory.

Comment on the rCBF technique

The mean hemispheric values and the regional landscapes obtained in our study, averaged across all groups and subjects, are in full agreement with previous studies (e.g. [14, 22-24], despite differences in number and location of detectors. Our data on the variation of mean hemispheric flows are perfectly supported by the data supplied by BLAUENSTEIN *et al.* [25]: They reported a standard deviation of about 6.5 for ISI and about 8.9 for f_g , almost identical to our corresponding values of 6.3 and 9.1. Regionally, we cannot directly compare our variance data to previous reports since those are based on fewer detectors which were concentrated in the center of the hemisphere.

As to the effects of habituation to the measurement situation, several previous reports showed that the resting mean flows decrease from first to second measurement (e.g. [5, 11, 14]). The present data show the same trend, but also show that blood flows increase during later measurements. The dramatic decrease of variance from first to second measurement, along with the flow level changes, suggest the following interpretation: Some people react quite strongly to the measurement situation; this reaction increases their mean blood flow in both hemispheres (but especially in the left premotor region, which will be discussed in more detail further on). All subjects are relaxed and habituated during the second measurement, and the usual level of cognitive activity is resumed at later stages, or perhaps boredom and immobility stress intensify it. The true baseline state for rCBF measurements seems, therefore, to be the second rest measurement. With the exception of this "second run effect", however, our results show that with sufficient care a considerable long-term stability of CBF can be achieved.

Neuropsychological implications

The frontal lobes. We have no definite explanations for the typical resting CBF pattern; some artifactual explanations have been dismissed by WILKINSON *et al.* [22], who concluded that the pattern was genuine, but its reasons obscure. Regarding hyperfrontality, INGVAR ([23] pp. 190-191), MEYER ([24] p. 357), RISBERG *et al.* ([11] p. 796) and MAXIMILIAN *et al.* ([14] p. 30) suggest interpretations ranging from intention to action, through awareness and general control of behavior, to stress, anxiety and emotional factors. Structural-anatomical explanations are possible, but not impressive; the relation between neuronal packing density and regional blood flow is weak [23, 26] and a functional hypothesis is likely to weigh heavily in the explanation. In a recent publication [27] INGVAR deals with hyperfrontality

and ascribes it to "inner anticipatory programming of several alternative behavioural modes prepared to be used depending upon what will happen". It is here proposed that this description is far too narrow and, furthermore, that an explanation is hardly necessary. There is considerable evidence [28-30] that anesthesia can abolish the normal hyperfrontality or even create a different fronto-temporal focus of increased activity. Although the frontal lobes of man are still largely mysterious, there is no doubt that they mediate several functions intimately concerned with maintenance of arousal, high-level cognition and general control of behaviour [21, 31, 32]. In a situation with no external stimuli or demands it is hardly surprising, then, that maximal activity is registered in areas responsible for maintaining the general structure of our behaviour. It should also be pointed out that rCBF methods cannot distinguish between excitation-inducing and inhibition-inducing activity, that at least some areas of the frontal-orbital region are involved in inhibition of autonomic and somatomotor activity [33], and that possibly our subjects spend some of their time trying to obey instructions by inhibiting natural reactions to talk, move, scratch, etc.

There are further intriguing related subjects that should be elucidated by further research. The first is the changes of frontal activity that occur with psychological and neurological activation procedures. An examination of the literature (some of which is referred to here) has shown that when other areas of the cortex increase their activity, the frontal increases are rather unpredictable, sometimes exceeding and sometimes being lower than the rest of the hemisphere. Previous work has come up with some indications [11, 14, 34, 35], but we are far from understanding the conditions that increase or decrease frontal activity in relation to the rest of the hemisphere. The question is perhaps identical with another: how much of frontal lobe activity is task-specific, and how much it is generally related to effort, arousal, etc. And the question may, of course, be directed at any structures within the frontal lobes, some of which may be associated with specific activities and others with general control (cf. [11, 14]). Support for the heterogeneous composition of frontal activities comes from examination of two high-resolution rCBF studies [27, 36]; they seem to show one or two distinct foci instead of a widespread uniform frontal activity. The clearest and most intense is in the premotor region (and, possibly, more so in the left hemisphere); the other apparent focus, seemingly weaker, is in the orbital region. These data show surprising correspondence to the areas that showed habituation in the present study, also in the left hemisphere. This could shed more light on frontal lobe functioning during "rest", considering the strong brain-stem connections of the orbital region, and the role of the supplementary motor area in verbal activities. The left premotor area is also distinguished in our study by its highly asymmetrical variance. Its activity in our measurement situation can be associated with general control and arousal or with verbal-mode cognition. A recent report of its importance in motor control [37] may be relevant, as well. Our data, however, do indicate a more significant role for this area than currently thought.

Lateral asymmetries and handedness

Most previous authors did not report significant lateral differences on either flow levels or variation, and possibly have not tested for them. BROOKS *et al.* [38], in a study of five right-handed and five left-handed subjects, show that the right hemisphere is about 9% higher than the left in the right-handed and about 13% higher in the left-handed. CARMON *et al.* [39], measuring cerebral blood volume in 60 right-handed and 25 left-handed and ambidextrous subjects (assessed by a manual preference test) reported that blood volume was higher in the right hemisphere of the right-handed and in the left hemisphere of the

left-handed. Our finding of higher right mean flow in the general right-handed sample is in good agreement with the previous ones. We show, however, that higher right-handedness is associated with higher right hemisphere flow, whereas BROOKS *et al.* showed higher R-L differences for left-handers. This apparent contradiction is well explained by THOMAS and CAMPOS [40] who showed that the degree of handedness, not its direction, is related to differences in performance. This can be extended to cortical organization: The subjects with high R-L differences in the Brooks study were left-handed, whereas those in our study with low differences were weakly right-handed. The mixed population in the CARMON *et al.* [43] study, and the known heterogeneity of cerebral dominance in left-handed subjects [41], do not allow definitive conclusions.

Regionally, f_g shows in the present study higher temporal flows on the left side (detectors 8L & 14L) and higher occipital flow on the right (detector 16R). Significant asymmetries of variation in the same direction are seen in occipital and posterior temporal areas, in addition to a much higher variance in the left premotor region. We consider these asymmetries to agree well with current concepts of hemispheric specialization, with the right-dominant visual functioning and left-dominant temporal functions, the precise nature of which is still debated (see PROHOVNIK [41] for a review). It is tempting to interpret these asymmetries as indications of localized information processing in our measurement situation, but that is probably unjustified. The pattern of inter-hemispheric asymmetries of f_g is not fully in agreement with our ISI flow results (Table 1), although there is no direct contradiction and they agree on variance asymmetries. The explanation is probably the different sensitivity of these two indices to very fast flows in small amounts of tissue [16] and we believe that a full explanation will be provided by a new analysis method that is currently undergoing final tests [42].

Relations of local rCBF asymmetries with handedness were found to be positive in superior frontal areas (and non-significantly, over the whole frontal lobe) and around the superior-posterior temporal area (detectors 11, 14, 16). The relationship seemed negative in the temporal lobe (detectors 8, 10, 12). These findings are in contrast to our expectations, and we cannot at present explain them. Nor can we find a non-artifactual explanation for the asymmetries of grey matter weight. Several authors have reported anatomical asymmetries in and around the sylvian fissure [41], and these may be related to our finding of temporal w_g asymmetries. There is, however, no report of anatomical asymmetries that are so uniform along the vertex. Additionally, the topographical distribution of these asymmetries seems quite artificial because of its uniformity, corresponding more to pure spatial factors than to a neuropsychologically meaningful pattern of the human cortex. We have also performed a factor analysis on our results and found two strong factors in w_g with loadings corresponding to the asymmetry pattern. The w_g asymmetries should therefore be interpreted with much caution, especially since this parameter is known to be less reliable, mathematically, than f_g and ISI.

The coordination of bilateral information processing. The pattern of homologous correlations described here, perhaps the existence of any pattern at all, has never before been shown or suspected as far as we know (but cf. [43]). We have found support, however, in others' data. BLAUENSTEIN *et al.* [25] present interhemispheric correlations and discuss them from the point of view of crosstalk. Upon examination of their HPFD correlations (corresponding to our distribution values) we found that they agree very well with our results, despite the small number of detectors they used. We have examined several explanations, for example:

(1) Hypotheses based on differences of variance in different regions, specifically explaining low correlations by high random variation or very small ranges. Some of the high-correlation regions, however, are among the peripheral ones with the highest variance and some show small ranges of variation. If these hypotheses were true there would be a typically high or low variance in the primary areas and an opposite situation in the association areas. This is not supported by the data: Variance distribution does not seem to be related to levels of processing.

(2) Higher cross-talk in high-correlation areas. Cross-talk refers to the possibility of each detector "looking into" the contralateral hemisphere. The influence of cross-talk has been shown to be rather unimpressive by other authors [25] and in any case it should be correlated to local width of brain, clearly not the case with our high correlations.

(3) Anatomical coupling explanations. The primary projection areas are directly and/or efficiently coupled by anatomical paths across the midline, whereas such paths do not exist, or do to a much lesser extent, for association areas. A search of the neuroanatomical literature resulted in no support for this assumption. Moreover, this pattern of homologous correlations disappears with activation (we checked with problem-solving tasks in the visual and auditory modalities). Thus the simple static anatomical explanation would not suffice even if such paths existed. A functional explanation is needed.

The explanation that best fits our data, and that we accept, is based on functional coupling. Information processing during our "rest" situation probably consists of simple, routine stimuli which do not require high-level activity and do not command attention (e.g. unarousing proprioceptive-somesthetic stimuli), and daydreaming of some kind, possibly a cognitive evaluation of the situation and/or emotional adjustments. It is likely that the simple low-level sensation analysis is performed equally and simultaneously by appropriate areas (projection, and perhaps secondary) in both hemispheres; the higher-level mentation, on the other hand, may be done in the two hemispheres independently of each other [41]. Thus, simple sensori-motor activities are bilaterally shared but each hemisphere's association areas are free to engage in their own unilateral (or laterally dominant) higher-associative processes. This functional model is consistent with the intermediate correlations in secondary areas, and we suggest it is the most plausible explanation. The general principle that emerges seems to be that the functional covariation, or coupling, between homologous areas (at least during our resting conditions) is inversely related to the level of processing that is associated with those areas.

That some parts of a human cerebral hemisphere can process data independently (more or less) of the other hemisphere has been fairly well documented [44]. Most of the work, however, has shown hemispheric dissociation of relatively simple perceptual-motor processes. For example, MOSKOVITCH *et al.* [45] tested manual reaction times to faces appearing in the right or left visual fields, the task being to compare members of a pair of faces either to each other or to a previously presented pair. The main result was that a consistent left-field superiority was absent for at least the first 50 msec following stimulus disappearance. The authors conclude that precategorical perception can be effectively accomplished by both hemispheres, and that both probably have access to a common (or double) immediate-recall register that contains the results of earlier processing; hemispheric advantages occur only at a later stage of processing, in temporal terms after about 100 msec.

Considerable theoretical advances in the elucidation of the "levels of processing" models of human cognition, learning and attention have been recently published [46, 47]. We propose that SCHNEIDER and SHIFFRIN's [47] "Automatic Processing" fairly well describes

the nature of processing imposed by our measurement situation: "Automatic processing is learned in long-term store, is triggered by appropriate inputs, and then operates independently of the subject's control. An automatic sequence can contain components that control information flow, attract attention, or govern overt responses. Automatic sequences do not require attention, though they may attract it if training is appropriate, and they do not use up short-term capacity." (p. 51). Our rCBF findings perhaps serve to topographically map on the cortex the temporal dimension of MOSKOVITCH *et al.* and the conceptual space of SCHNEIDER and SHIFFRIN. Low-level processing, thus, is accomplished jointly by appropriate low-level areas of both hemispheres with very short delays from stimulus occurrence; high-level areas are free to engage in other activities which are not necessarily co-ordinated bilaterally. A demand for high-level processing will spread the activity temporally and spatially within each hemisphere, create homologous covariation in at least some high-level areas and probably abolish it at least in some low-level areas. The issue of hyperfrontal rCBF at rest, then, should perhaps be regarded as an issue of "hyperfrontalities", as the two lobes are possibly not concerned with the same functions in this situation.

Of equal theoretical importance is the lack of negative homologous correlations. Among the attempts to explain the mode of inter-hemispheric interaction in the human brain [41] one approach, outstanding in its coherence and scope, is KINSBOURNE's. Among KINSBOURNE's basic postulates we can find the assumption of mutual inhibition on the regional level: "Areas of cortex that subserve specific functions inhibit other areas which are potentially capable of that same function" ([48] p. 261). Do the lack of negative correlations in our data contradict this assumption? The high positive correlations in primary areas do not contradict the mutual inhibition hypothesis, since it may relate only to areas involved in higher levels of processing. In association areas, however, the hypothesis would predict negative correlations instead of the observed zero correlations. We can resolve this difficulty by assuming that KINSBOURNE's model should be restricted to demand situations, i.e. with tasks imposing high-level processing or in SCHNEIDER and SHIFFRIN's apt terminology "controlled processing". Most likely, we can confirm or discard this model only when task-related loads approach the upper limits of available attention.

Finally, there is considerable empirical evidence that the two cerebral hemispheres may compete for attentional and behavioural control [41, 49]. Why, then, the very high correlations shown here between the mean blood flow of the two hemispheres? The first explanation has already been invoked: even global competition between the hemispheres probably applies only in controlled-processing situations; this idea emerges quite naturally from an examination of experimental situations employed to provoke this competition. Furthermore, it should be pointed out that the vascular systems of the two hemispheres are far from separate, that a unilateral lesion often reduces activity and blood flow contralaterally [50], and that the diffuse excitatory or inhibitory influence of brain stem structures (probably reflected in our mean hemispheric flows) can be bilaterally shared, even after total commissurotomy [51]. Differential activation or suppression of the cerebral hemispheres will, thus, be shown only by small differences in their mean blood flows (cf. [10]) and even then they will be highly correlated.

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Résumé :

On a mesuré bilatéralement le flux sanguin cérébral régional (FSCr) de 16 régions corticales chez 22 adultes sains avec des mesures répétées 4 à 8 fois par individu. Toutes les mesures étaient faites durant le "repos" c'est-à-dire avec des stimulations externes minimales, par la méthode d'inhalation Xe-133. Ces données sont présentées non seulement pour servir de contrôle pour le travail clinique et de recherche mais surtout en raison de leur signification pour une théorie neuropsychologique. Quelques variations du FSCr paraissent significativement liées à la préférence manuelle, aux processus d'habituation, aux rythmes biologiques et peut être à la dominance latérale régionale. D'autres données permettent d'envisager le rôle possible des structures frontales durant les processus cognitifs en dehors des épreuves. Enfin, on considère que ces données montrent que le couplage fonctionnel régional à travers la ligne médiane est inversement lié aux caractéristiques du niveau de traitement correspondant à chacune des aires.

Zusammenfassung:

rCBF wurde bilateral für 16 corticale Regionen bei 22 gesunden Erwachsenen gemessen, 4-8 wiederholte Messungen pro Versuchsperson. Alle Messungen wurden in Ruhe, d.h. unter geringster äußerer Stimulation, mit der Xe-133-Inhalations-Methode, vorgenommen.

Die Daten werden als Grundlage für experimentelle und klinische Arbeiten mitgeteilt, besonders aber wegen deren Bedeutung für neuropsychologische Theoriebildung. Einige rCBF-Unterschiede haben Beziehung zu Händigkeit, Habitierungsprozessen, biologischen Rhythmen und möglicherweise zu regionaler lateralisierter Dominanz. Weitere Daten und Erörterungen haben Beziehung zur möglichen Bedeutung von Frontallappenstrukturen während Wahrnehmungsvorgängen, die nicht auf ein bestimmtes Ziel gerichtet sind. Schließlich werden die Daten so interpretiert, daß sie zeigen, wie die Zusammenkoppelung von umschriebenen Hirnregionen über die Mittellinie in diese Situation in umgekehrter Weise zu dem charakteristischen Niveau der Bearbeitung jeder Region in Beziehung steht.

REGIONAL CORTICAL ACTIVITY DURING PERCEPTION:
VISUAL TASKS OF INCREASING COMPLEXITY

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ABSTRACT

Cerebral blood flow determinations, mirroring cortical activity, were made in 32 cortical regions of 8 normal subjects during three conditions of visual stimulation, using rest with closed eyes as base-line. Visual stimulation was achieved by a Spiral-After-Effect (SAE) apparatus and the three conditions were: looking at a stationary spiral, looking at a rotating spiral, and performing the SAE test. Average cortical flow increases during these conditions were 5%, 7%, and 12%, respectively. Local activation was seen in occipital, parietal, temporal and frontal regions; both the magnitude and spread of local flow increases were related to task complexity. The results are in agreement with anatomical degeneration studies of visual pathways and other animal studies showing a sequential processing hierarchy. Hemispheric flow asymmetries, probably unique to man, are reported and discussed and a hypothesis is suggested to describe a sequential oscillation of asymmetries, depending on task complexity.

Cortical loci of visual information processing have been indirectly mapped by degeneration studies showing a pathway from the striate cortex to the circumstriate cortex, the inferior temporal lobule and parts of the frontal lobe (Jones & Powell, 1970). Most studies of the functional significance of these areas have relied on behavioural observations following ablation (Kikuchi & Iwai, 1980) and single-unit recordings (Gross et al., 1979) in primates. Recent methodological advances have even allowed direct measurements of metabolic activity in small cerebral regions during visual stimulation. Using the ^{14}C -deoxyglucose technique Kennedy et al. (1976) and Shinohara et al. (1979) studied cortical glucose metabolism in monkeys who were looking at moving stimuli or performing a visual discrimination task. The results confirmed the presence of a visual pathway from the striate cortex, through the circumstriate and the inferior temporal lobe to the temporal pole. The structures which were activated included "tissue adjacent to the inferior temporal cortex in the upper bank of the superior temporal sulcus, and in the fusiform and perirhinal areas", and subcortically "lateral and dorsal amygdala, ventral putamen, ventral claustrum and tail of the caudate" (Shinohara et al., 1979). These and other studies support a sequential, hierarchical model of visual perception (Mishkin, 1966).

The results cited so far have all been limited to animal studies. The need for studies in man is, however, obvious; both the functional organization of the cerebral cortex

and the typical level of complexity of information processing may be radically different, making generalizations of animal results questionable. Although some initial attempts have been made to measure local glucose metabolism of the cortex in man during visual stimulation (Reivich et al., 1979), most of the data available are based on measurements of regional Cerebral Blood Flow (rCBF). The results from rCBF studies might, however, be interpreted as equivalent to metabolic data since it has been shown that the regional blood flow of a normal brain is closely coupled to, and can be regarded as an index of, local metabolic activity (Raichle et al., 1976; Greenberg et al., 1979).

Interesting observations in man have been reported by Cooper et al. (1965) who studied occipital blood flow in two epileptic patients by means of implanted electrodes. They found an increase of blood flow in the striate cortex (area 17) during both flicker stimulation and reading, while area 18 and 19 showed marked elevations of flow during reading but no changes during flicker. Melamed and Larsen (1977) studied unilateral rCBF in patients during eye opening and conjugate gaze shifts, by means of the intra-carotid ^{133}Xe injection technique and a high-resolution detector system. They found that opening the eyes (looking at a cross shape) increased hemispheric blood flow by 8%. Locally they found a 25% flow increase in "temporo-occipital visual cortex (area 19)" and a 14% increase in the motor strip and adjacent premotor frontal cortex. During eye movements, induced by having the patient follow a moving

object, they found the same increase in area 19 and a 20% increase in the frontal eye fields and also elevations in the supplementary motor area. Several other studies of rCBF changes during mental activity have used the visual modality for presentation of information but none have been aimed at studying the visual perceptual process per se (but c.f. Risberg et al., 1975). The present investigation was intended to study bilateral rCBF in normal subjects during visual information processing of increasing complexity. The stimulus used was a spiral which was either stationary, rotating or intermittently replaced by circle for experience of the Spiral-After-Effect (SAE). The rCBF-measurements were made by the non-invasive ^{133}Xe inhalation method which is especially suitable for repeated, bilateral measurements in normal subjects.

MATERIAL AND METHODS

Subjects

The measurements were made in eight young (mean age 23 ± 2 years) healthy male volunteers (students and hospital employees). They were all right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971).

The rCBF measurements

The measurement technique is based on inhalation, during one minute, of a mixture of air with the inert and freely diffusible gamma-emitting tracer ^{133}Xe ; during this minute the tracer diffuses into brain tissue from arterial blood (Obrist et al., 1975). During the following 10

minutes the subject breathes normal air, the tracer diffuses back into venous blood and is cleared through the lungs. The gamma radiation from the brain and the respiratory air is continuously monitored by external scintillation detectors. Calculations of rCBF are based on Fourier analysis of the brain curves, expressed as the f_1 flow index, which represents flow of grey matter (in ml/100g/min). For details of the analytical model, its solutions and technical procedures, the reader is referred to recent publications (Obrist et al., 1975; Risberg, 1980; Jablonski, et al. and Prohovnik et al., in press). In our laboratory, radiation is monitored bilaterally by 32 detectors and processed by a standard rCBF system (NOVO Diagnostic Systems, Hadsund, Denmark). Average detector locations for one hemisphere are shown in Fig 1.



Figure 1. Average detector localization over homologous regions of the cerebral hemispheres. The central and lateral fissures are shown for reference.

Our placement procedure has recently been described (Prohovnik et al., 1980) and the approximate location of our detectors in relation to brain contours has been con-

firmed by skull x-rays in five patients. Data from the rCBF system were recorded on paper punch or on a micro-computer-controlled disk (Ohio Scientific). Hewlett-Packard 9825 and Ohio Scientific C3 computers were used for flow calculations, graphics and statistical analysis.

The experimental conditions

Four rCBF-measurements were made in each subject during the following experimental conditions (the order of conditions was randomized):

1. Rest. The subject was lying supine with closed eyes and instructed to relax without falling asleep.
2. Stationary Spiral (StSp). The field of view of the subject was limited by the eye-piece of a modified Spiral-After-Effect (SAE) apparatus. The spiral was a black 2.5-turn arithmetic spiral (12 cm diameter) on a white background, drawn with a 1 mm line, observed at an apparent distance of 90 cm. In the StSp condition the subject was only instructed to keep his eyes open.
3. Rotating Spiral (RotSp). This condition was identical to StSp except that the spiral was now rotating at 120rpm. The subject was only required to keep his eyes open.
4. Spiral-After-Effect (SAE). The subject was instructed to fixate the center of the rotating spiral for 15 or 30 sec after which time the spiral was replaced by a circle (6 cm in diameter and drawn with a 2 mm line). The replacement was accomplished by a system of mirrors and illumination switches and was very rapid and virtually soundless. The subject was instructed to report

(by saying "now") the termination of the illusion, which was a centrifugal or centripetal motion of circle boundaries according to direction of rotation. Immediately after this response the spiral was switched on again. All the activation procedures were started one minute before the start of ^{133}Xe breathing and continued for 8 minutes. All subjects performed three practice trials of the SAE condition before the start of the measurement. They all detected the illusion spontaneously.

Statistical methods

The statistical analysis was primarily based on one-way analysis of variance for repeated measurements. In addition, product-moment correlations and t-test for related means and variances were applied to check for hemispheric asymmetries. Significant asymmetries will be described by referring to the side with higher flow.

RESULTS

Regional flow values, hemispheric mean values and their variances are shown in table 1 for all four conditions. During resting the mean hemispheric values were 76 and 75 ml/100g/min for the right and left hemispheres respectively. This level increased by 5% during StSp, by 7% during RotSp and by about 12% during SAE. Thus, the more complex the level of processing the larger the rCBF response. The mean hemispheric increases were approximately equal between the hemispheres. The flow changes can not be explained by changes of arterial pCO_2 , since these values were very

Table 1. Mean flows (and standard deviations) in 32 cortical regions and averaged in both hemispheres. Eight subjects during four conditions. Mean pCO_2 for each conditions is also given.

Condition :

	REST	StSp	RotSp	SAE
Det. nr				
1R	79 (8)	82 (11)	84 (8)	89 (11)
2R	79 (8)	85 (13)	83 (9)	91 (14)
3R	94 (10)	94 (13)	96 (7)	102 (12)
4R	82 (7)	87 (11)	88 (10)	93 (15)
5R	78 (5)	84 (11)	85 (9)	88 (12)
6R	80 (9)	81 (8)	83 (10)	87 (10)
7R	79 (8)	83 (10)	80 (8)	84 (12)
8R	77 (7)	78 (7)	84 (8)	89 (9)
9R	71 (6)	75 (10)	75 (9)	81 (12)
10R	70 (6)	75 (8)	74 (8)	80 (11)
11R	72 (7)	78 (10)	79 (7)	83 (13)
12R	68 (8)	71 (9)	73 (7)	73 (7)
13R	68 (7)	73 (11)	73 (8)	77 (12)
14R	68 (5)	71 (6)	74 (5)	77 (10)
15R	67 (5)	73 (8)	75 (5)	77 (10)
16R	81 (10)	87 (8)	89 (10)	90 (13)
1L	77 (7)	82 (15)	83 (8)	88 (13)
2L	78 (8)	82 (13)	82 (9)	86 (15)
3L	92 (10)	91 (7)	93 (7)	98 (10)
4L	82 (8)	86 (12)	87 (8)	90 (13)
5L	75 (8)	82 (12)	83 (9)	85 (16)
6L	80 (13)	81 (9)	83 (9)	87 (10)
7L	77 (9)	78 (11)	80 (6)	83 (15)
8L	76 (10)	77 (10)	78 (6)	83 (10)
9L	70 (6)	71 (10)	75 (7)	77 (10)
10L	71 (7)	77 (10)	73 (7)	77 (12)
11L	74 (8)	77 (11)	78 (9)	82 (12)
12L	63 (8)	67 (9)	69 (5)	72 (13)
13L	65 (8)	70 (11)	72 (7)	73 (13)
14L	70 (7)	76 (7)	76 (6)	81 (9)
15L	69 (5)	73 (10)	76 (6)	78 (11)
16L	85 (12)	87 (9)	94 (15)	95 (14)
Mean R	76 (5)	80 (9)	81 (6)	85 (10)
Mean L	75 (6)	79 (9)	80 (5)	83 (11)
pCO_2	42.2	42.4	42.1	42.6

stable and within the normo-capnic range (mean 42 ± 4 mm Hg) throughout the measurement series. The blood pressure was also normal and very stable in the group (MABP 97 ± 7 mm Hg).

The resting pattern

Regional flow variation around the hemispheric averages during rest is shown in Fig. 2. The well-known frontal flow elevation ("hyperfrontality") is evident.

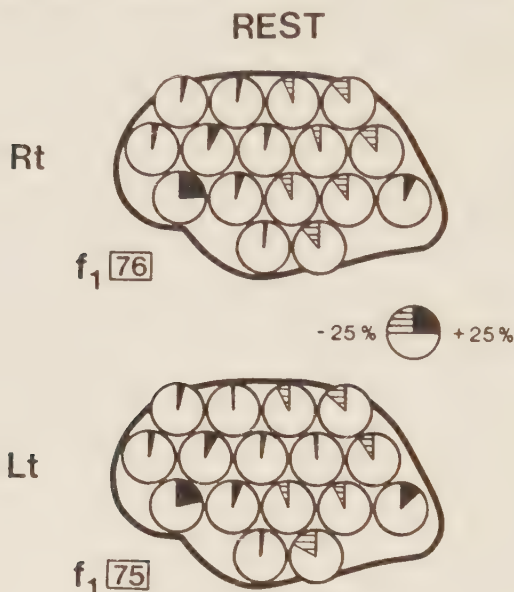


Figure 2. The resting flow pattern in eight subjects. Hemispheric means are shown in boxes; each regional flow is expressed as % deviation from its hemispheric mean. Black fields in the clock symbols denote values above hemispheric means and striped denote values below hemispheric mean ($25\% = 90^\circ$).

The peak at the fronto-orbital position is possibly due to an artifactual overestimation of flow in this area, caused by imperfect correction of the influence from ^{133}Xe in the air passages. The resting flow patterns in the two hemispheres are generally very similar, but asymmetries were noted in left inferior parietal (11L) and right inferior temporal (12R) areas.

The activation responses

Figure 3 illustrates the rCBF increases from rest to the three visual conditions. A rather weak activation response was found during StSp, with activity foci in parietal-occipital (especially right), posterior temporal (especially left) and superior frontal (probably supplementary motor) areas. Activation was nearly absent in anterior temporal and fronto-orbital regions. Flows in posterior parietal and Rolandic areas were significantly higher on the right (13R, 7R, 9R), as was the mean hemispheric flow. Only one region, posterior temporal (14L) was higher in the left hemisphere.

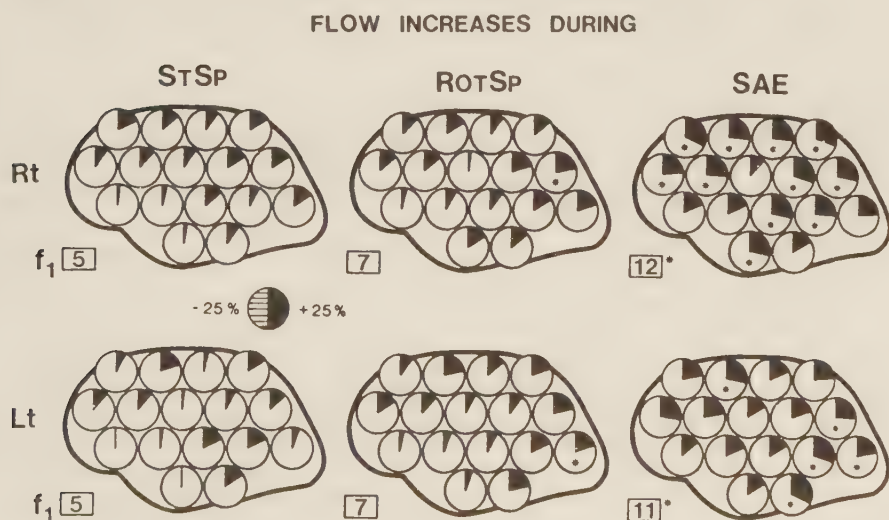


Figure 3. Flow changes from rest for the three visual conditions (%) in 8 subjects. Mean hemispheric changes are shown in boxes, regional changes as clock symbols. A black field denotes increase from rest, striped denotes decrease, ($25\% = 180^\circ$). The asterisks show a significant change ($p < .05$), by ANOVA and Scheffé test.

During RotSp there was no obvious change in the activation pattern (Fig. 3), all regions having slightly increased their activity compared to StSp.

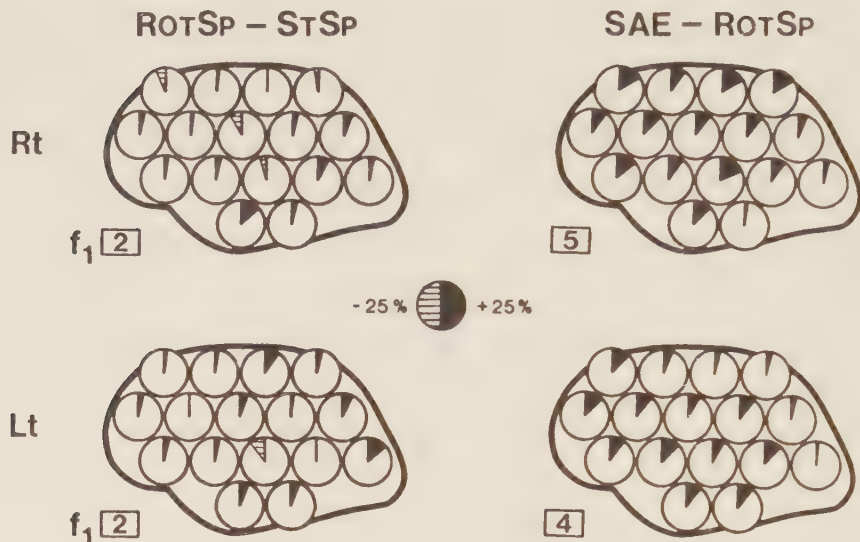


Figure 4. Relative changes of flow among the visual conditions in 8 subjects. Each value was computed as the difference of increases from rest between two visual conditions: Symbols as in fig. 3.

Figure 4 indicates, however, that rotating the spiral had the effect of balancing the activity in the two hemispheres, the main changes from StSp being in right temporo-occipital and left parieto-occipital areas. During this condition flow is significantly asymmetric in right inferior temporal (8R & 12R) and premotor region (5R) and left posterior temporal area (14L). The StSp asymmetries in parietal and Rolandic regions, as well as in hemispheric means, have disappeared.

In contrast to the similarity between StSp and RotSp, the SAE caused rCBF increases that were about twice as large as the previous ones. The largest increases in relation to RotSp (Fig. 4) were in frontal, anterior temporal and right central-parietal regions. The smallest changes occurred in occipital and left central-parietal areas, where this condition apparently adds very little to the activation due to the rotating spiral. The activation response is generally slightly larger on the right side: mean hemispheric flow asymmetry is just below significance and the asymmetries are significant in posterior parietal (13R) and anterior temporal (8R) areas. The left hemisphere is still significantly higher in a posterior temporal region (14L), as it was in the other visual conditions.

To be clinically useful as activation procedures, effects must be reliable on an individual basis in addition to being significant as group results; we therefore checked the interindividual consistency of increases, defined as flow changes of +1% or more. During StSp the effects were about random. During RotSp three occipital locations (14R, 15L, 16R) showed increases in all eight subjects. The SAE activation was better, with six regions and the right hemispheric mean flow showing increases in all subjects. The uniformly increasing regions were frontal (1L & 4R), anterior temporal (8R), inferior parietal (11R) and occipital (14R & 16L). Further examination showed that seven of the eight subjects consistently increased their flow in both hemispheric means and nine additional regions, mostly frontal (1R, 2R, 3L, 5R, 5L, 6L, 9R, 13L, 14R). The eighth,

deviant, subject had high resting flows and practically no increases during activation. Aside from a slightly higher blood pressure and the shortest SAE duration (average of 4.7 seconds) there was nothing-remarkable about him, and no medical or technical reason to exclude him. His results are therefore included in all analyses and figures.

Finally, it should be mentioned that direction of spiral rotation was randomized across subjects, but double determinations (both directions) were performed in four subjects. In those four a counterclockwise rotating spiral (contracting, with an expanding after-effect) elicited higher flows, especially in right frontal and temporo-occipital regions, and longer after-effect durations (7.5 Vs 5 seconds), compared to a clockwise rotation. These findings were not significant due to the small material.

DISCUSSION

As mentioned in the method section, the results presented here are based on the f_1 flow parameter derived by the new Fourier analysis. A full comparison of flow analyses and parameters is outside the scope of this article, but it should be mentioned that the common analysis (Obrist et al., 1975), done in parallel on these data, yielded similar but much weaker effects (especially during SAE). This sensitivity difference is most probably due to the utilization, by Fourier analysis, of the total information in the clearance curves, whereas the conventional analysis virtually ignores the first 90-120 seconds. This initial period

contains information about the flow in small activated tissue volumes. The high sensitivity of Fourier analysis is shown, however, not only by its superiority to the conventional analysis but also by its similarity to the results of the most sensitive carotid injection method. Our StSp condition is equivalent to Melamed and Larsen's open eyes condition, and with the exception of the occipital pole and parietal lobe areas our results may well be taken as a good replication of theirs. The occipital pole area is practically invisible to that technique, but the parietal lobe deserves further comment.

Shinohara et al. (1979) did not describe any parietal involvement either, but neither they nor Melamed and Larsen present the data to be examined, and neither specifically mentioned this areas. We have found quite robust effects parietally, especially in our detector 13, roughly corresponding to Brodmann's area 7. Jones and Powell found no degeneration in this area after ablations of the cortical visual pathways, but the existence of light-sensitive neurones in area 7 is known (Mountcastle, 1978). Moreover, there is highly convincing evidence for visual functions of this area (Warrington and Rabin, 1970; Hassler, 1972; Kuypers, 1978; Van Essen, 1979) as well as more general spatial orientation and discrimination functions (Pohl, 1973; Butters et al., 1972; Mishkin, 1979). Possibly, the two successive increases in this areas in our study represent two different functions, one simple and modality-specific (bilaterally symmetric, during StSp) and one more complex and integrative (right hemisphere, during SAE).

The asymmetric response of the posterior parietal region during SAE is part of the general asymmetry issue in this study. It is tempting to speculate on the well-documented right hemisphere dominance for visual-spatial processing (reviewed in Prohovnik, 1978), seen here as local and mean hemispheric flow asymmetries during StSp and SAE. It is also interesting to note that much of this asymmetry disappeared during RotSp. One might consider reasons such as increased eye movements and the left hemisphere dominance for at least some forms of motor control (Haaland et al., 1977; Lomas, 1980). Alternatively, we would speculatively propose a working hypothesis of stepwise saturation of functional asymmetries. According to this hypothesis, human information processing may be thought of as a stepwise continuum. A very simple task, such as our StSp, is processed with a certain amount of functional asymmetry; when the task is made more difficult or complex without qualitatively changing, e.g. RotSp, these asymmetries tend to weaken or disappear as more cerebral resources are recruited. At a certain level of complexity the resources are fully occupied; if the task is then made still more difficult, another arrangement of functional organization is achieved, qualitatively different from the previous one, and asymmetries may again appear. Reasonably, the new level of organization may be associated with a quantitative leap of general arousal, as the SAE in our study was associated with a large general increase in flow levels. Thus, the SAE flow asymmetries would be caused by a high-level spatial discrimination problem, the StSp asymmetries by the presumed dominance of the right hemisphere for visual

perception per se (Kimura & Durnford, 1974), and the weakened asymmetry during RotSp by partial saturation of low-level visual perception mechanisms.

The specific visual projection to the frontal lobes shown by Jones and Powell (1970) was not seen in monkeys by Shinohara et al. (1979). Our results indicate two components of visual-frontal activation: One during StSp, corresponding to Melamed and Larsen's (1977), and another, superimposed, during SAE. It seems that the latter component is not modality-specific, since it is not found during RotSp which must account for a large proportion of the visual stimulation during SAE. Since, compared to RotSp, the SAE showed considerable frontal increases, these are likely to be associated with other task components, such as decision-making and readiness to respond; similar nonspecific frontal activation has been indicated before with rCBF (Risberg et al., 1977). The relation of SAE to arousal (Holland, 1965) and specifically to the CNV (Abraham and McCallum, 1973) is consistent with this interpretation.

Finally, a note on task-related and individual-related variance. Several early reports found that an expanding spiral-after-effect was seen for longer durations than a contracting one by normals and was easier for "brain damaged" to perceive (Holland, 1965). We found this duration effect, and also a somewhat different and higher flow response. The effect was consistent in our four subjects, but small and nonsignificant. On the other hand, we found a highly disturbing interindividual variance component in

that one of our subjects showed virtually no rCBF increases due to visual stimulation. Our sample was admittedly small, and we do not know how unusual this phenomenon may be. Research in rCBF has only very recently begun to elucidate some individual differences as related to handedness (Prohovnik et al., 1980), characteristic eye movement direction, and task performance (Gur & Reivich, 1980). Until more material is available, the SAE may be used cautiously with rCBF as an activator of large cortical parts, especially frontal and parietal areas.

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REGIONAL CORTICAL ACTIVITY DURING PERCEPTION:
LATERALIZED TACTILE SENSATION AND ATTENTION

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ABSTRACT

Measurements of regional Cerebral Blood Flow (rCBF) were made on 10 subjects during rest and tactile stimulation of the right hand, left hand, and both. In a sensation condition the subjects were encouraged to ignore the stimulation, whereas in the attention condition (with identical stimuli) the subjects monitored either hand or both in a vigilance task. Sensation was reflected in parietal and prefrontal flow increases contralateral to stimulation. Attention to the right hand mainly enhanced right hemisphere flow, in the same areas. Attention to the left hand, and bilateral attention, were associated with much larger, diffuse flow increases in both hemispheres. These results support recent proposals of right hemisphere dominance for some forms of attentional activation.

The elegant study by Jones and Powell (1970) contrasted three cortical pathways, corresponding to the main sensory modalities, by means of the sequential degeneration technique in the monkey brain. In a previous study we (Prohovnik et al., this volume) demonstrated the functional equivalent of the anatomical visual pathway, defined by measurements of the regional Cerebral Blood Flow (rCBF) in normal man; rCBF is known to reflect metabolic activity in the normal brain (Raichle et al., 1976; Greenberg et al., 1979). In the present study we similarly investigated the tactile modality, in an attempt to verify in man the models proposed by Jones and Powell (1970) and Mishkin (1979) on the basis of animal studies. The anatomical data indicate a projection from the postcentral gyrus to the secondary sensory area (SII), the precentral gyrus and the anterior parietal area 5. Area 5 then projects to area 6 frontally and area 7 parietally, and area 7 connects more extensively with the frontal lobe and with an area in the depth of the superior temporal sulcus, in addition to its limbic projections. Two previous attempts to measure cortical blood flow during somesthesia have been published. Ingvar et al. (1976) used electrical stimulation of the thumb and recorded mostly frontal flow responses, and Roland and Larsen (1976) used a complex stereognostic task with a motor component (active palpation) and found flow increases in the Rolandic hand area and in a superior frontal region. These studies, however, used the carotid injection method and were therefore limited to unilateral measurements in patients remitted to angiography. The present study of normal subjects was intended to maximally utilize the bilaterality

of the ^{133}Xe inhalation technique. A major path for tactile information from the hand is known to ascend through the dorsal spinal column, the cuneate tract and nucleus, cross to the contralateral thalamus in the medial lemniscus and then project to the primary somatosensory area, SI (Semmes, 1973). We attempted to see this major contralateral component by measuring rCBF bilaterally during tactile simulation of the right and left hand.

Another important design principle was the isolation of components of complex processing. We employed identical tactile stimuli in two cognitive conditions termed sensation (stimulation with no required processing) and attention (same stimulation, with a simple perceptual task and instructions to ensure attending). The study was conducted as two separate experiments, one with unilateral stimulations and the other bilateral.

EXPERIMENT I

Material and Methods

Five normal subjects, students and hospital employees, were studied. They were all male (aged 21, 22, 25, 28, 48), right-handed (by the Edinburgh Handedness Inventory, Oldfield, 1971) and healthy (by medical history). The rCBF measurements were done by a standard system (NOVO Diagnostic Systems, Hadsund, Denmark) with 16 detectors covering each cerebral hemisphere (fig. 1). For further details see the previous article (Prohovnik et al., this volume).

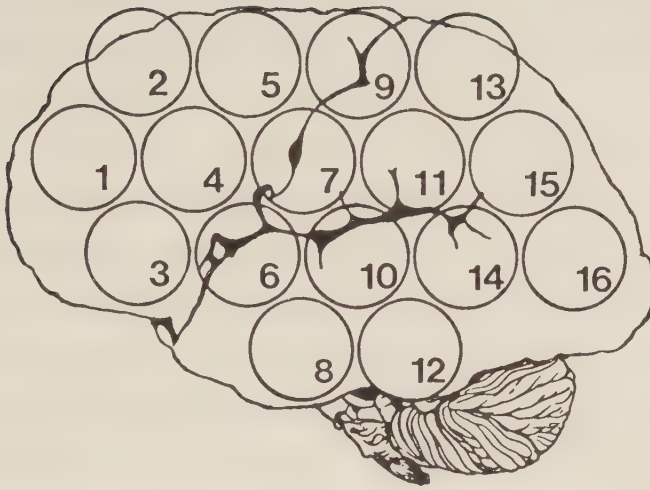


Figure 1. Average detector localization over homologous regions of the cerebral hemispheres. The central and lateral fissures are shown for reference.

Tactile stimulator

Basic principles of stimulator construction were similar to those suggested by Carmon and Dyson (1967). Stimulation was achieved by nine aluminum pins arranged in a square 3x3 array with 10 mm center-to-center distance; their ends were shaped as truncated cones, with a diameter of 1 mm. These pins were kept up and away from the subject's hand by a vacuum housing. When stimulation was desired, the vacuum was replaced by compressed air, the pressure of which could be regulated. Any number and pattern of pins could be selected. When activated, they were pressed against the skin for a duration which could be adjusted with about one second precision. A standard list of 80

stimulation patterns was used for both hands and both conditions. Sixteen patterns consisted of one pin only, the rest involving 2-5 pins. All combinations were evenly distributed over all pin locations with randomized order.

Design and Procedure

The factorial design consisted of two cognitive conditions (sensation and attention) and two stimulation sides (right hand and left hand), with randomized order. The four resulting conditions are accordingly termed SensRt, SensLt, AttRt and AttLt. Each subject was measured during rest (baseline without stimulation) and during four tactile conditions (one subject had only sensation for technical reasons). Stimuli during all conditions were identical, consisting of the standard list, and no learning effect could be found by performance and self-reports, reflecting the large number and similarity of stimuli. The subjects' eyes were closed throughout all conditions.

After the rCBF procedure was thoroughly explained, the subject lay on the bed and his hand was placed on a rubber cushion in a comfortable position, dorsal side up (the stimulated side). The stimulator was placed about 2 mm above the skin. Instructions for the Sens conditions included only encouragement to relax and ignore the stimuli. For the attention conditions, the subjects were instructed to carefully monitor all stimuli on the chosen side and respond to the target patterns (one pin only) by saying "one". Before the first stimulation for each subject the instrument was explained and demonstrated, and a rough

threshold determination was quickly done. Stimulus pressure and duration were adjusted to achieve approximately 50% performance on a more difficult discrimination task, to avoid ceiling effects (no subject subsequently had perfect performance). Before each attention condition the subjects received training trials with feedback; no feedback was provided during the rCBF measurement. Average stimulus duration across subjects was 5 sec and pin pressure varied from 35 to 60g. Stimulation began 30 sec before the start of ^{133}Xe inhalation and continued for at least 10 minutes. Depending on stimulus durations, subjects received from 70 to 130 stimuli.

RESULTS

Figure 2 illustrates flow responses during the sensation condition, compared to the resting pattern which was very similar to the one in the previous article (Prohovnik et al., this volume). The largest flow increases occurred in prefrontal and parietal regions (especially detectors 2 and 13); these were also the regions with the clearest contralateral responses, i.e., they showed larger responses contralaterally to the stimulated hand than ipsilaterally. Figure 3 shows the contralateral increases, derived by subtracting the two ipsilateral increases from the two contralateral (for both Sens conditions). An interesting observation is also the apparent involvement of the right posterior parietal area (13R) in both SensRt and SensLt. During SensRt flow was significantly asymmetric in detectors 2L,

6R and 13L and during SensLt in 2R, 5R, 7R and 13R.

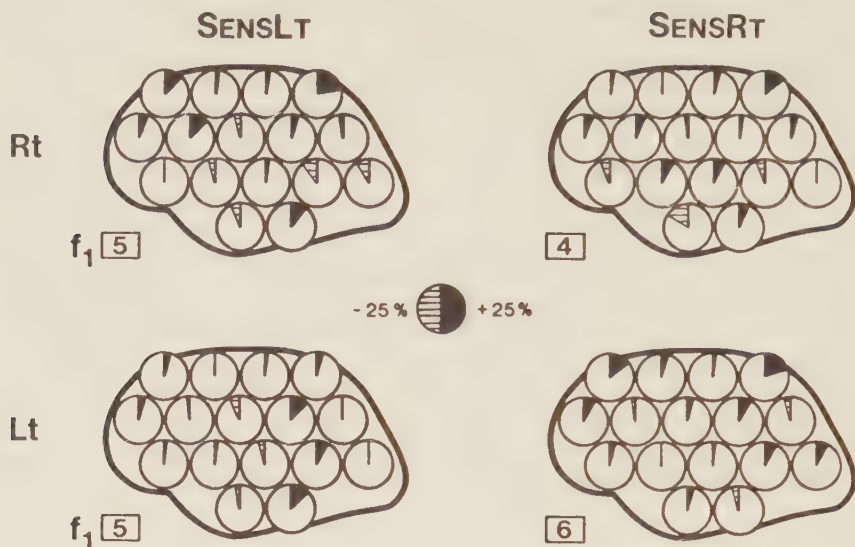


Figure 2. Average increases of flow (%) from rest to the sensation conditions (SensLt, SensRt) in five subjects. Number in boxes denote mean hemispheric increases and clock symbols show increases as black, decreases as striped ($25\% = 180^\circ$). The asterisks show a significant increase ($p < .05$), by ANOVA and the Scheffé test.

SENS CONTRALATERAL

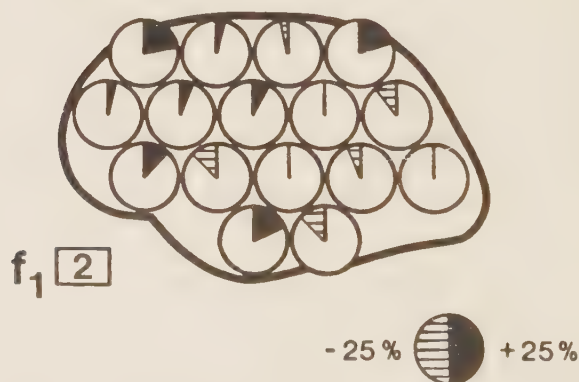


Figure 3. Increases from rest of the hemisphere ipsilateral to the stimulated hand were subtracted from increases of the contralateral hemisphere in five subjects; data were averaged over both sensation conditions. Note the somatosensory hand area in the mid-Rolandic region (detector7). Symbols as in fig. 2.

The attention conditions yielded a remarkably different result; flow increases from the respective sensation conditions are shown in figure 4. If attention induces an additive increase of cortical metabolism beyond the sensation-associated component, it should be visible here. Comparing AttRt to SensRt, attention clearly enhanced flow mainly in the right hemisphere, and in areas very similar to the ones that showed activation by sensation alone, parietally and frontally. In the left hemisphere, changes occurred mainly in and around the temporal lobe, and activation is on the average no stronger than due to sensation alone. Flow was higher in the right hemisphere, significantly in frontal (2R, 3R, 4R), Rolandic (6R, 7R) and parietal (13R) regions, as was mean hemispheric flow.

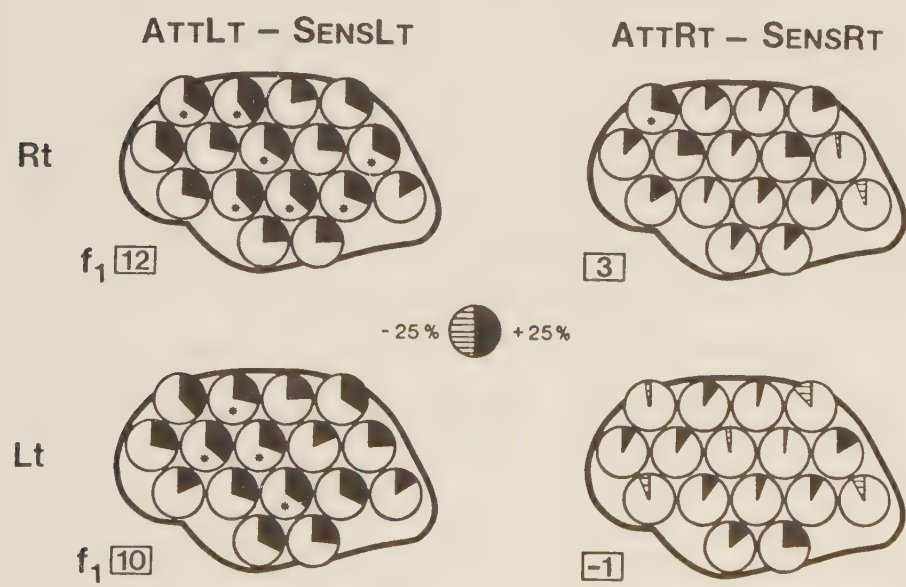


Figure 4. Sensation-associated flow increases subtracted from Attention-associated increases in five subjects. Symbols as in fig. 2.

AttLt, on the other hand, resulted in an intense widespread activation of both hemispheres, but again with a right hemispheric advantage. Mean hemispheric flow again significantly higher in the right, as it was in four regions (1R, 7R, 8R, 13R). Performance was better with the left hand (16% errors, vs. 20% for the right hand) but the difference did not reach significance.

DISCUSSION

Both sensation conditions and AttRt yielded results that were easy to integrate with current knowledge. The magnitude of AttLt effects, however, constituted a major surprise. Several sources of error could be postulated, based on the inevitably inexact nature of manual test administration and the unilateral apparatus. To name a few, the relative freedom of the hands could allow movements during stimulation and reduce reproducibility of hand position relative to the pins. There was a possibility of auditory cues related to the number of activated pins, and of course there was the possibility of experimenter bias, since all adjustments and controls were manually done by us. Finally, the dorsal stimulation site is rather unusual and unnatural, possibly adding unknown variables. We therefore decided to construct an improved version of the stimulator and repeat the experiment with bilateral stimulation. Since the results were very similar, we combined the experiments in the general discussion.

EXPERIMENT II

Five male subjects were again studied. Their ages were 21, 24, 25, 26 and 31 years and they were all right-handed and healthy by the same criteria as for experiment I.

Tactile stimulator

A second stimulation unit was constructed, identical to the first. Each unit was now built into a transparent plastic box, which also had three short tunnels for the fingers and two straps (one at the wrist and one just distally to the thumb); these ensured a stable and reproducible position of both hands in relation to the pins. Stimulation site was now changed to the middle of the palm, with the hands resting on the boxes, palms down. Stimulation time was held constant for both hands in all conditions at 7 sec (with a 1 msec precision). Individual thresholds were determined as before, but only pressure was adjusted, varying for the five subjects between 40 to 50g. Stimulation was quiet, always bilateral, and fully controlled by a Hewlett-Packard 9825 computer.

Design and Procedure

A list of 100 stimuli was prepared in five blocks of 20. This list included 19 target stimuli (one pin only), the rest varying between two and seven. All were about equally distributed among the five blocks, randomized within blocks and among pin positions (i.e., position of stimulation on the palm). Another list was then prepared by randomly re-

arranging the stimuli within each block, but constrained so that an identical stimulus was never present in the same place for both lists. These lists were incorporated into the computer program.

In addition to rest, the experimental conditions were again AttRt and AttLt with the same perceptual task as in the first experiment. In four of the subjects we added a condition of bilateral attention (AttBi), during which the subjects were instructed to attend and report stimuli from both hands simultaneously. Both hands were always stimulated, and physical components of the stimulation system (electronic, pneumatic and mechanical) were randomly interchanged between the left and right hands.

RESULTS

Performance was again better in the AttLt conditions than in AttRt (6% errors vs. 9%, $t=5.48$, $p<.01$). Blood flow increases from rest during AttRt and AttLt are shown in Figure 5 for four of the five subjects, for comparison with the AttBi condition. The difference between AttRt and AttLt, although not as dramatic as in the first experiment, was very similar and significant. We have therefore combined these results into one group of 10 subjects, summarized in table 1 and depicted in figure 6. The resting pattern was very similar to the one in the previous article (Prohovnik et al., this volume). AttRt is here seen to be associated with parietal and frontal increases in both hemispheres, but predominantly in the right; the apparently

higher increase in the left posterior temporal region actually reflects an asymmetry during rest.

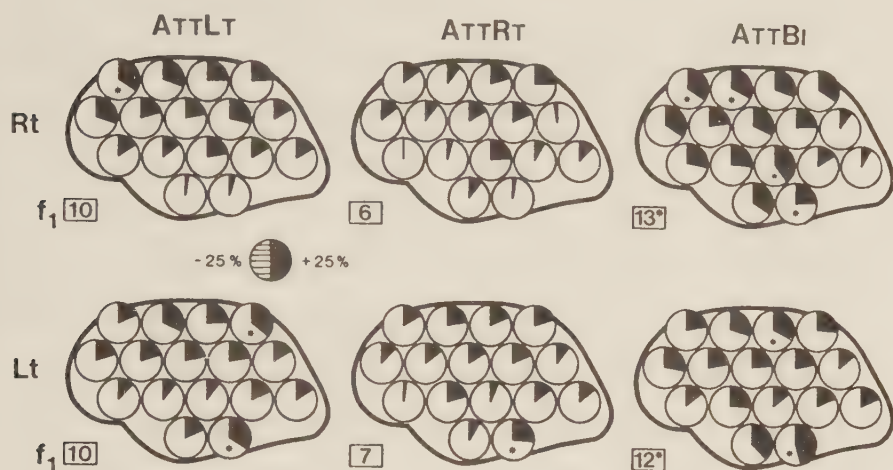


Figure 5. Average increases of flow (%) from rest to three Attention conditions in four subjects. Symbols as in fig.2.

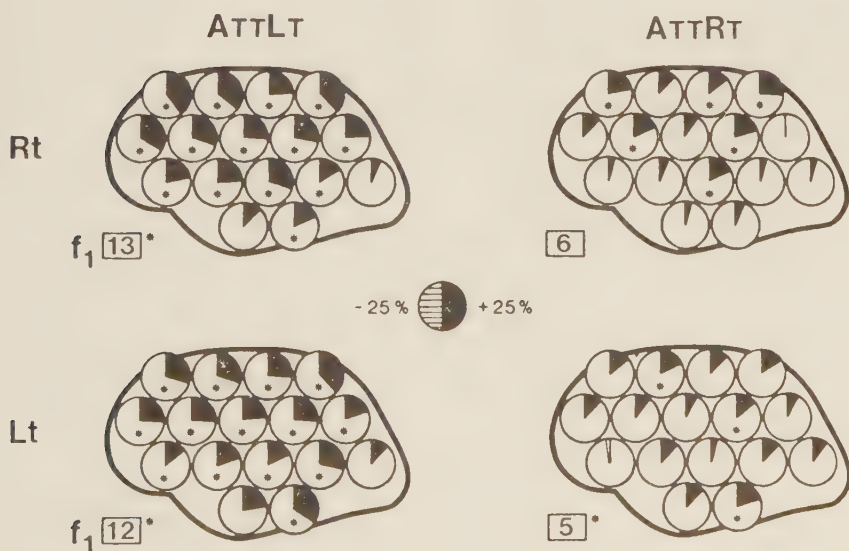


Figure 6. Average increases of flow (%) from rest to AttLt and AttRt in all 10 subjects. Symbols as in fig. 2.

Table 1. Mean flows (and standard deviations) in 32 cortical regions and averaged in both hemispheres. Ten subjects during three conditions. Mean pCO_2 for each conditions is also given.

Condition:

	REST	Att Rt	Att Lt
Det. nr			
1R	73 (10)	77 (12)	85 (15)
2R	70 (11)	78 (11)	84 (14)
3R	85 (15)	86 (12)	94 (16)
4R	76 (12)	83 (14)	87 (16)
5R	73 (10)	78 (12)	86 (16)
6R	72 (10)	74 (10)	80 (13)
7R	71 (9)	74 (9)	80 (13)
8R	75 (8)	77 (11)	80 (13)
9R	67 (10)	71 (8)	75 (12)
10R	62 (10)	68 (8)	71 (10)
11R	65 (9)	71 (11)	74 (9)
12R	64 (13)	66 (8)	69 (9)
13R	62 (11)	69 (10)	73 (15)
14R	63 (6)	65 (6)	69 (6)
15R	62 (9)	62 (8)	69 (11)
16R	77 (13)	79 (13)	79 (10)
1L	72 (11)	77 (10)	81 (13)
2L	71 (10)	76 (12)	82 (17)
3L	85 (12)	84 (13)	91 (13)
4L	76 (11)	79 (13)	86 (14)
5L	70 (10)	77 (11)	81 (14)
6L	71 (12)	74 (11)	78 (11)
7L	69 (10)	72 (11)	77 (13)
8L	68 (14)	72 (12)	75 (14)
9L	67 (8)	71 (13)	75 (11)
10L	65 (8)	66 (9)	71 (11)
11L	66 (9)	71 (11)	74 (11)
12L	59 (9)	65 (8)	69 (10)
13L	60 (9)	65 (11)	72 (15)
14L	62 (7)	65 (7)	70 (11)
15L	62 (9)	65 (9)	68 (9)
16L	73 (15)	76 (11)	77 (9)
Mean R	70 (9)	74 (11)	79 (12)
Mean L	68 (9)	72 (10)	77 (12)
pCO_2 mm Hg	41.1	41.5	41.2

AttLt, however, obviously induces a different state of the brain. Similarly to AttRt it is more intense in the right hemisphere, and the major increases are again seen in parietal and frontal regions. But superimposed on this pattern there is a general, diffuse activation of the whole brain which is associated with increases from rest twice as large as during AttRt.

Finally, performance during AttBi was equally good in both hands and as good as the right hand during AttRt (9% errors). Flow increases are somewhat larger than during AttLt, much larger than during AttRt (fig. 5). Comparing AttBi to AttLt, the main differences are seen in temporal and inferior frontal regions.

GENERAL DISCUSSION

We were not able to demonstrate clear focal rCBF increases in the primary somatosensory projection area. This is probably due to the small size of the area, rather than to any insensitivity inherent in the inhalation method, since Ingvar et al. (1976), using carotid injection and 32 detectors covering one hemisphere, did not see any clear primary increases, whereas Roland and Larsen (1976) recorded distinct focal increases with 254 detectors. With our present resolution we could, however, see relatively large increases in frontal and parietal association areas, predominating contralaterally to the stimulated hand. These results agree well with previous studies, described in the introduction, but the extent and localization of flow increases

indicate that we were measuring a state more complex than pure sensation. The asymmetric engagement of the right parietal area also supports this interpretation. This area has previously been seen to be activated by the Street test of perceptual closure (Risberg et al., 1975), a complex jigsaw puzzle test (Berglund et al., 1980) and Spiral-After-Effect (Prohovnik et al., this volume). Strangely enough, Roland and Larsen (1976) could not demonstrate any changes in this area during a complex stereognostic task; we have, at present, no explanation for this discrepancy.

Obviously, the sensation condition was not devoid of attentional components and it was impossible to ensure complete disregard of the stimuli: They were, from the subjects' point of view, the only occurrences of interest during the measurement. The difference between what we called sensation and attention can be expressed as non-task oriented, automatic, evoked orienting to stimuli (c.f. Berlyne, 1969) vs. volitional, motivated, vigilance performance. We use the term attention rather than vigilance to stress the main theoretical point of the study. Since the two attention conditions were identical in all stimulus and task variables, the only difference being the volitional selection of perceptual channels, the term attention in its selective sense is highly appropriate (Posner and Boies, 1971). We can compare the attention conditions to sensation, thus defining the effect of perceptual vigilance within a channel, and we can compare the attention conditions to each other, thus defining selective attention between channels within the task.

To discuss the effects of perceptual vigilance first, we use the sensation conditions as control. During sensation, we demonstrated contralateral increases up to 11% in parietal and frontal areas and no major dominance of either hemisphere. In this we confirm earlier studies that found no hemispheric dominance for the simple, low-level aspects of tactile perception (Corkin, 1978). Perceptual vigilance was clearly found to change this cortical activity pattern with an additional component during AttLt. Since the AttLt condition confounds both effects, it might be argued that only a comparison of AttRt to SensRt shows the difference between sensation and active perception. This comparison was shown (fig.4) to emphasize right parietal and frontal regions similar to the ones activated by sensation, but more intense and widespread during the attention task. The left hemisphere showed increases mostly in and around the temporal lobe, and was considerably less activated than the right. The small number of subjects and the theoretically diffuse definition of the cognitive difference between the conditions make any attempt at a rigorous interpretation hazardous, but we may speculate a little further on anatomical findings. It would seem that the activation spread parietally to the inferior lobule, possibly area 40, which does not exist in animals. Frontally it seems to be strongest in an area roughly corresponding to 8 and 9, and then extend ventrally through areas 45 and 46 to the orbital area. In any case, we may conclude that a hemispheric asymmetry emerged here, that the right hemisphere is more activated by our task, and that the regional activation pattern induced by the attentional or active-

perceptual demands was certainly different in the two hemispheres.

The major finding of the present study, however, is that attention to the right hand is much less activating, for both hemispheres, than attention to the left hand. This was found in two separate experiments, one with unilateral stimulation and one bilateral. In both experiments there was no difference whatsoever in the imposed task or stimulus variables for the two conditions, nor any possible effect of systemic physiological variables as reflected in arterial $p\text{CO}_2$ and blood pressure. The only difference between the two conditions was the direction of selective attention during the same task, and the effect cannot be attributed to asymmetry for lower processing as shown during the sensation conditions. This unexpected finding led us to a reexamination of the literature, which revealed considerable indirect support.

Two highly relevant studies in normal subjects have recently been published. Heilman and Van Den Abell (1979 , 1980) tested 24 subjects in a simple reaction time paradigm, with foreperiod. The warning stimuli signalling the foreperiod were, however, selectively projected (by means of lateralized visual fields) to the right or left hemisphere. Left visual field warning stimuli (right hemisphere) reduced reaction time significantly more than right-field warning stimuli. Moreover, EEG desynchronisation (defined as decrease in alpha power) occurred in the left parietal lobe only with right field warning stimuli, whereas the right

parietal lobe desynchronized equally to right or left warning stimuli. In the second study, Bowers and Heilman (1980) used basically the same design, but with verbal (word) or spatial (face) warning stimuli which were centrally projected. As with the EEG data, verbal warnings reduced reaction time differentially in the right hand whereas there was no significant difference between the hands with warning stimuli composed of faces. Examination of the data reveals some puzzling aspects, however. The main effect seems to be that the right hand with verbal warning is considerably faster than all other combinations, which are only minimally different from one another. In the Heilman and Van Den Abell (1979) study, it was again the right hand, but with left visual field warning, that showed the largest reaction time reduction and contributed most to the effects. The general finding of right hemisphere dominance agrees well, however, with our findings and is supported by much clinical evidence, some of which will now be described.

Howes and Boller (1975) studied 49 patients with unilateral lesions and no ipsilateral motor impairment, compared to 16 matched hospitalized non-neurological patients and 16 normal subjects. The test consisted of simple reaction time to auditory clicks, with all controls using their right (preferred) hand and all patients using the hand ipsilateral to the lesion. Lesion size was estimated from brain scans, and was found to be somewhat larger in the left hemisphere. In spite of this, reaction time was clearly worse with right hemisphere lesions (635 msec) than with

left (334 msec); both groups were impaired, compared to the controls (215 msec). On the basis of the scans, the authors suggested possible involvement in the right hemisphere of the posterior parietal area and the basal ganglia. Dimond (1976) studied six commissurotomed patients during a lateralized vigilance task and found a clear right hemisphere superiority, the left hemisphere often suffering attentional lapses and missing long periods of signals. Finally, there is much clinical evidence for the dominant involvement of the human right hemisphere in the unilateral neglect syndrome (Weinstein and Friedland, 1977). Heilman and Watson (1978) showed, for example, that verbal tasks cause more severe neglect than visuospatial ones. On the basis of these and other findings, they proposed a general model of neglect.

The model proposed by Heilman and his collaborators (c.f. Heilman and Watson, 1977; Heilman and Watson, 1978; Heilman and Van Den Abell, 1980) considers the neglect syndrome a unilateral defect in the orienting response. It usually arises from lesions of the inferior parietal lobe, dorsolateral frontal cortex or cingulate gyrus. These areas are critical parts of a cortic limbic-reticular loop, which exists in each hemisphere and is crucial for the orienting response, but is dominated by the right hemisphere. The right hemisphere can arouse the left via interhemispheric pathways, but not vice versa (Bowers and Heilman, 1980). The precise theoretical nature of this putative right-hemisphere dominance does not seem to be defined, but mainly these authors refer to Sokolov's orienting reflex model and

to what Pribram and McGuinness (1975) called activation, i.e., tonic physiological readiness to respond. The neural system mediating activation was hypothesized by Pribram and McGuinness to center on the basal ganglia.

We propose that the effects seen in the present study during lateralized attention are similar to the ones Heilman and collaborators suggested for the neglect syndrome. We would, however, propose that the reticular aspect is at least as likely as interhemispheric commissures to mediate the suggested dominance. Zernicki et al. (1970) showed in cats that the mesencephalic reticular formation is predominantly controlled by the ipsilateral hemisphere, although its output is largely bilateral. The right hemisphere, thus, does not need to excite or inhibit the left; its activation affects the reticular system, which then distributes it to both sides.

Actually, there is some confusion in the literature about the appropriate terminology. Sokolov's model mainly pertains to the phasic component of data input (Sokolov, 1975), termed arousal by Pribram and McGuinness, who consider its neural substrate to center on the amygdala. Hassler (1978) describes a construct similar to Pribram and McGuinness' activation, but calls it vigilance and describes its major neural components as the rostral midbrain reticular system and the posterior hypothalamus. However, Hassler (1978) describes another substrate for directed attention which is very reminiscent of our findings and related ones. According to Hassler, directed attention does

center on the basal ganglia, especially the Pallidum, and several thalamic nuclei. The cortical components of this complex circuit are the premotor and orbital frontal regions and the parietal areas 5 and 7; Hassler emphasizes the "contraversive" nature of this attentional circuit. It seems that despite terminological confusion our findings agree with other evidence, and with hypothesized models, in indicating a system including parts of the parietal and frontal lobe. This system mediates some form of lateralized activation or attention, and is dominant in the right hemisphere; we assume that activation of the whole brain is modulated and controlled by its reciprocal connections with the reticular system. In this context it is interesting to mention the rCBF study of finger movements by Halsey et al. (1979). These authors found a more prominent response for left hand movement than for right hand. They thought the difference might reflect different motor organisation of the hemispheres or the difficulty of fine motor control of the non-preferred hand. In light of our findings and this discussion, we propose that the effect found by Halsey et al. was similar to ours, i.e., that attention to the left hand is more activating than attention to the right hand. To confirm this, we analysed our data also with the conventional analysis (Obrist et al., 1975) used by Halsey et al. The results were somewhat less dramatic than with the new Fourier analysis, but fully in agreement: Mean hemispheric flow increased 7-8% during AttRt, compared to 11-12% during AttLt. Thus, their results may be interpreted as showing the same activation effects as ours, elicited by a sensorimotor task rather than a

purely sensory one.

Finally, a comment about our bilateral attention condition. This condition is commonly referred to as distributed attention, as opposed to selective or focused attention (Kahneman, 1973). Performance of both hands in this condition was equal to performance during AttRt, and slightly worse than during AttLt. Cortical activation, however, exceeded the intensity seen during AttLt and was much higher than during AttRt. This combination of large flow increases without corresponding enhancement of performance is commonly taken as a sign of difficulty. Common sense and general attention literature would support this interpretation (Kahneman, 1973) but it has been shown to be misleading in at least some forms of tactile perception (Shiffrin et al., 1973). Our results on four subjects indicated that the main regional flow differences between AttLt and AttBi, which presumably share the same general activation factor attributable to right hemispheric arousal, occurred in both temporal lobes, and especially in their anterior parts. This pattern is reminiscent of Pribram and McGuinness' (1975) so-called effort system, centering on the hippocampus and related structures. These authors ascribe to the effort system the function of coordinating arousal and activation, uncoupling the stimulus from the response and regulating "state", set or "attitude". It is admittedly very difficult to translate the operational variables of an experiment to psychologically meaningful verbalizations, as shown by these vague terms. Still, we think there is some value in suggesting the possibility that this hippocampal circuit

also coordinates the sharing and distribution of attention in our bilateral condition, as indicated by the anterior temporal increases which distinguish it from both unilateral attention conditions.

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